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The Effects of Boron on the Range of Motion of Dexterity Related Joints: A Patient with Rheumatoid Arthritis

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THE EFFECTS OF BORON ON THE RANGE OF MOTION OF DEXTERITY-
RELATED JOINTS: A PATIENT WITH RHEUMATOID ARTHRITIS

by

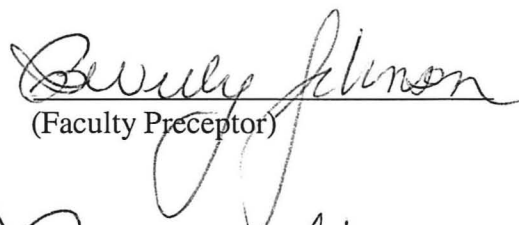
Nicole L. Herda and Jessica A. Woehl
Bachelor of Science in Physical Therapy
University of North Dakota, 2001

A Scholarly Project
Submitted to the Graduate Faculty of the
Department of Physical Therapy
School of Medicine
University of North Dakota
in partial fulfillment of the requirements
for the degree of
Master of Physical Therapy

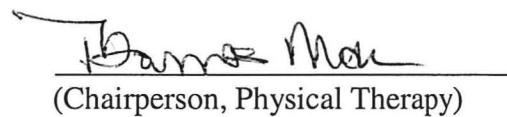
Grand Forks, North Dakota
May
2002



This Scholarly Project, submitted by Nicole L. Herda and Jessica A. Woehl in partial fulfillment of the requirements for the Degree of Master of Physical Therapy from the University of North Dakota, has been read by the Faculty Preceptor, Advisor, and Chairperson of Physical Therapy under whom the work has been done and is hereby approved.


(Faculty Preceptor)


(Graduate School Advisor)


(Chairperson, Physical Therapy)

PERMISSION

Title The Effects of Boron on Range of Motion in Dexterity-Related Joints in a Patient with Rheumatoid Arthritis

Department Physical Therapy

Degree Master of Physical Therapy

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Signature Nicole Herda

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Date 12/06/01

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Mostly, we thank God for the wonderful gifts He has blessed us with, especially the gift of Physical Therapy that will allow us to show His love by caring for our many future patients.

ABSTRACT

Rheumatoid arthritis is a progressive, destructive and chronic, inflammatory disease of the joint synovium. Signs and symptoms include pain, limited range of motion, swelling, and tenderness, which may progress to deformity. These manifestations may limit dexterity, independent living, and the overall well being of an individual. Living with daily restrictions proves to be a psychologically distressing experience.

An increase in the dietary boron level of laboratory rats has shown to have a positive effect on the range of motion in their involved joints. This concept was tested on a human subject at the United States Department of Agriculture's Human Nutrition Research Center in Grand Forks, North Dakota over a six-month period from January 9th to June 19th, 2001. Joint involvement was assessed using goniometric measurements, a Poly Arthritis form, along with palpation of 16 fibromyalgic points. Subjective information was compiled regarding subject's level of pain, stiffness, bogginess, and soreness. The subject was measured on a consistent day and time each week. The study was conducted under the direction of Dr. Curtiss Hunt at the Human Nutrition Research Center and Beverly Johnson PT, MS at the University of North Dakota Department of Physical Therapy. Institutional Review Board approval was obtained, and inter-rater and intra-rater reliability were established prior to testing. A standardized verbal instruction

regimen, to guide the subject and to encourage her to give her maximal effort during measurements, was used.

With an increased intake of boron, a significant influence on the range of motion was predicted. It was found, however, the active number of joints for this subject remained relatively constant, proving bogginess and soreness/sensitivity to palpation to still be present. However, the subjective rating of pain, fibromyalgic points, and hours of morning stiffness decreased with boron deprivation. By analyzing the range of motion statistics, 21 out of 64 tested motions were found to display changes in the measurements of dexterity-related joints for an individual with rheumatoid arthritis between boron supplementation and deprivation. A general increase was noted with boron supplementation, whereas a decrease was noted in the range of motion with boron deprivation.

The purpose of this case report was to analyze the effect of boron supplementation and deprivation and to aid in improving the pathological related signs and symptoms of an individual with rheumatoid arthritis. The potential to decrease the clinical manifestations and reduce the psychological stress of living with a chronic illness would benefit individuals with rheumatoid arthritis.

CHAPTER I

INTRODUCTION

“How far you go in life depends on you being tender with the young, compassionate with the aged, sympathetic with the striving, and tolerant of the weak and the strong. Because some day in life, you will have been all of these.” ~George Washington Carver

“Arthritis limits the activity of over 7 million people and tops heart disease as the leading cause of work disability.”¹ Estimates place medical care and lost wages to exceed 64 billion dollars annually. Rheumatoid arthritis, the most common form of inflammatory arthritis, affects 2.5 million Americans.² This accounts for approximately one percent of the population of the United States, roughly one in 100 people.³

“Rheumatoid arthritis affects approximately four times as many women as men, and symptoms are often first noticed by people between the ages of 25 and 50”. There is no evidence for environmental factors or an infectious etiology.⁴ At the present, the etiology remains unknown in the research of rheumatoid arthritis. It is known however, that it is a progressive, destructive, and chronic, inflammatory disease that affects the synovium and connective tissues of the joints.

The onset of rheumatoid arthritis is frequently insidious and gradual.⁴ Clinical features of rheumatoid arthritis are manifested in the early stages by joint pain and swelling in the metacarpophalangeal (MCP) and proximal interphalangeal (PIP) joints of the hands in a symmetric distribution. The distal interphalangeal joints are often spared. Rheumatoid arthritis is a systemic disease; therefore, as progression occurs most of the

body's joints are affected. However, the focus of our study was related to dexterity-related joints of the hands and wrist. Other affected joints will not be of relevance to this study.

Symptoms may include signs of pain, limited range of motion, stiffness, swelling, and tenderness.⁴ A duration of stiffness occurs after prolonged immobility, such as a night's rest, and is a common indication of the severity of the inflammation. The initial swelling, also referred to as bogginess, is due to an increase in the synovial fluid and may be fluctuant. Bogginess can also be characterized, in a more chronic stage, when the synovial lining proliferates.

With deterioration of the joints, rheumatoid arthritis may progress to deformity and loss of function. These manifestations may limit dexterity, independent living and overall well-being of an individual. Living with daily restrictions proves to be a psychologically distressing experience, especially when rheumatoid arthritis displays itself with other associated ailments.

Fibromyalgia often occurs in conjunction with rheumatoid arthritis.⁴ It is characterized by widespread pain and tenderness throughout the body present for a minimum of three months and meeting criteria of 11 or more of 18 specific muscular sites using approximately four kilograms of force.⁵ The pain resulting as secondary complications of rheumatoid arthritis can further limit the capabilities of the individual with rheumatoid arthritis.

Physical and psychological features are prevalent and interwoven in the lives of individuals with rheumatoid arthritis. As physical therapists, it is pertinent to understand

and monitor these factors to ensure quality care is given in a holistic manner. Treating a patient involves awareness of all factors affecting the client. A new approach in rheumatoid arthritis treatment may be through the use of boron supplementation. The significance of this case report is to demonstrate if a significant change is noted in the range of motion of dexterity-related joints in individuals with rheumatoid arthritis through boron supplementation. Clinically, as a team member, the therapist must be aware of the expanding current knowledge in treatment options to further assist individuals living with rheumatoid arthritis.

The purpose of this scholarly project is to assess the effects of a specified dosage of a boron supplement on the physical and emotional manifestations of rheumatoid arthritis. Furthermore and more inclusively, this project strived to answer the following questions: 1.) Is the range of motion affected in dexterity-related joints through the administration of boron? 2.) Is there a significant reduction of the boggiess and/or sensitivity of the dexterity-related joints when a specified level of boron supplement is governed? 3.) Does the number of active fibromyalgic points chosen from the assessment form significantly alter when boron is administered in a specified dosage? 4.) What impact do the physical and psychological aspects have on the physical therapy treatment of these individuals?

Previous research indicates that an increase in the dietary boron level has a positive effect on the range of motion of the affected joints in laboratory rats.⁶ The theory of boron's significance in the joints of humans with rheumatoid arthritis has not yet been investigated. We propose that factors influenced by the inflammatory process of

rheumatoid arthritis including active fibromyalgia points, boggiess, sensitivity, and range of motion of the dexterity-related joints of human subjects will be positively affected by the increase in dietary boron levels through supplementation.

CHAPTER II

REVIEW OF LITERATURE

Rheumatoid arthritis is a progressive and systemic disease causing deterioration of the joints.⁴ Fibrosis of the synovium often results, causing a decrease in range of motion, stiffness, swelling, and possible deformity of the affected joints. Clinical features of rheumatoid arthritis are manifested in the early stages by joint pain and swelling.

With rheumatoid arthritis, the inflammatory process occurring in the joints is also accompanied by deposition of immune complexes and rheumatoid factor in the synovial lining.⁴ The synovial lining provides nutritional sources to maintain joint function. As the inflammatory process repeatedly occurs, the lining proliferates, joint deformity occurs, and a loss of function results. The tendons and ligaments throughout the body become deprived of nutrients due to a limited supply of nutrients and therefore, weaken. This allows the dexterity-related joints of the hand to retain several deformities characteristic of rheumatoid arthritis. These deformities may include boutonniere, swan-neck deformity, ulnar deviation, and volar subluxation; collectively they will significantly interfere with hand function.⁴ The deformities can be debilitating to the patient's lifestyle. The medical field is exploring treatment options for pain management and to decrease the impact of functional impairment.

Evidence has recently supported that the mineral boron increases the range of

motion of the joints in laboratory rats and helps control the normal inflammatory process.⁷ In the only reported controlled human study of the interaction between boron, used as an oral dietary supplement, and inflammation, 20 patients with confirmed osteoarthritis received a placebo or six milligrams of boron for eight weeks in a double-blind trial.⁸ The arthritic individuals who received boron supplementation reported a significant improvement in subjective measures of their condition.

In 1995, Dr. Curtiss Hunt reported that “ample amounts of dietary boron compared to very low amounts significantly delayed the onset of adjuvant-induced arthritis in rats”.⁷ It was also demonstrated by Curtiss Hunt that “an animal model shows that physiological amounts of boron help control the normal inflammatory process.” During the latter mentioned, the rats were fed boron low or boron supplemented diets and had arthritis induced into the joints through injection of M. butyricum. Signs of inflammation and swelling were evident in the contralateral paw to a much greater degree with the boron low diet. This suggests that ample amounts of boron may decrease the inflammation in joints of laboratory rats. A study was recently initiated under the supervision of Dr. Hunt, at the North Dakota Department of Agriculture Human Nutrition and Research Center in Grand Forks, North Dakota to evaluate the effects of boron supplementation and deprivation in the human subject.

Boron is a micromineral, meaning that the body requires only small periodic amounts to fulfill its health needs.⁹ Boron is a trace mineral found in various foods that are consumed daily in the human diet. These include alcoholic beverages, almonds, apples, apricots, asparagus, avocados, beets, broccoli, brussel sprouts, cabbage, carrots,

cherries, dandelions, dill seed, figs, grape jelly, hazelnuts, legumes, parsley, peaches, peanuts, pears, poppy seed, strawberries, squash, and tomatoes.^{8,9,10} Age and gender differences may vary according to the necessary estimated daily intakes. The Recommended Daily Allowance established by the Food and Drug Administration is set at three milligrams.⁸ Care must be taken when preparing boron-rich foods, as boiling in water or oil quickly decreases boron content. A daily intake of three milligrams of boron has been suggested by The Rheumatoid Disease Foundation to assist in treating both osteoarthritis and rheumatoid arthritis.¹²

Other uses of boron have been researched. Boron has the ability to replicate estrogen in the body.⁸ As little as three milligrams of boron in the blood has been proven to double circulating estrogen levels.¹² This increase in estrogen may relieve multiple menopausal symptoms.^{9, 12} Boron may play a role in osteoarthritis prevention due to the ability to replicate estrogen in the body. Osteoporosis may be prevented due to boron's capability to overcome low vitamin D₃ levels and prevent bone demineralization. Research has also shown that boron may be effective in improving immunology by decreasing enzyme activity.¹⁰ Mental alertness has been associated with boron-rich diets.⁹ It is apparent that boron may play a vital role in many physiologic activities.

Boron toxicity, however, is another topic that may need to be addressed with the individual with rheumatoid arthritis. Signs of acute boron toxicity include the following: nausea, diarrhea, vomiting, headache, hypothermia, weariness, erythema, restlessness, renal injury, and death.¹⁰ Excess boron changes the acidity within the system, resulting in a loss of electrolyte balance within the body. Consuming excessive amounts of boron

around levels of 18-20 grams has proven to be toxic to the human body, however a minimal lethal dose has not yet been established.

The use of boron should not be used as the solitaire treatment. If found to be effective, it should be used in conjunction with other treatments. Physical therapy is a main component of this multidimensional approach. Treating the individual with rheumatoid arthritis may include, but is not limited to, the following: massage, aquatic therapy, strengthening, range of motion, aerobic activities, splinting to prevent contractures, joint protection, and gait analysis. Exercise has been stated in literature to have variable effects on the disease progression within the joint;^{13, 14, 15} dynamic exercise has been proven beneficial for the preservation of joint integrity.¹⁶

Anti-inflammatory medication is a vital component to decreasing joint destruction and ultimately, deformity for patients with rheumatoid arthritis. As physical therapists, it is vital to educate the patient on energy conservation techniques^{17,18,19} and joint protection²⁰. "Joint protection aims to reduce pain and local inflammation, preserve the integrity of joint structures and improve function."²⁰ Less traditional treatment interventions that patients may combine with their physical therapy intervention in controlling their arthritis include herbal remedies²¹, massage, acupuncture, and COX-II Inhibitors²².

By obtaining background knowledge in the rapidly changing medical research related to rheumatoid arthritis it will allow for ultimate physical therapy care of individuals with rheumatoid arthritis. The therapist may assist them in questions they

may have regarding upcoming treatment approaches, referral to proper professionals in treatment and nutrition, and supply information regarding nutritional values.

CHAPTER III

METHODOLOGY

Final approval for this scholarly project was granted by the University of North Dakota and the United States Department of Agriculture's Human Nutrition Research Center in Grand Forks, North Dakota. A copy of the University of North Dakota Human Subjects Review Form and specific testing procedures from the USDA Human Nutrition Research Center, Grand Forks, North Dakota are included in Appendix C.

Subjects

Participants were selected through the USDA Human Nutrition Research Center and criteria for this selection can be found in the Participant section of the Human Subjects Review Form in Appendix C. Participants were to be women who do not smoke or consume alcohol and were diagnosed with chronic rheumatoid arthritis by a physician using standard diagnostic procedural criteria. Participation in this study was completely voluntary and could be terminated at the request of the subject. An honorarium of \$5,580.00 was given for participation in the study. The subject was housed at the USDA Human Nutrition Research Center in Grand Forks, North Dakota for a total of 168 days during the time period of January 3rd, 2001 through June 21st, 2001. Two subjects participated in the study initially, however one subject terminated her participation after six weeks.

A statistical power analysis was conducted; it determined 14 subjects were needed for a power of 95% to demonstrate significant ($\alpha=0.05$) treatment effects. See Appendix C.

Therefore, information from this case report cannot be generalized to the population, and results must be viewed as an $n=1$. The subject receiving boron supplementation in this case report was 49 years old at the time of data collection. She wore bilateral wrist splints that kept her wrist in approximately 20 degrees of extension with slight radial deviation for joint protection. At this facility, the subject was monitored 24 hours a day in conjunction with the Human Nutritional Center's policy for subjects to assure appropriate experimental control and strict compliance with diet. See Appendix C for the IRB.

The subject was assessed on several clinical tests to measure the psychological, physiological, and biomechanical effects of the boron supplementation or deprivation on a routine basis. Some of these assessments included the following: hand volume water displacement, a psychological questionnaire, medications taken, a nursing assessment, and a self-assessment form. Physical therapy was responsible for taking measurements with joint assessment, range of motion, fibromyalgic points, pain scales, and an active joint count. This case report will be limited to measurements performed by the physical therapist and the related data.

Dietary Boron Supplementation

Boron content of the diet of our subject was regulated at a basal diet level of 2.0 milligrams per 2000 kilocalorie for the first 14 days. The estimated boron consumption per day of women 60-65 years old is 0.731 milligram. The estimation of 1.95 milligram is considered the 95th percentile of women ages 19 and older. See Appendix C. Over the course of the next 77 days, the subject received a diet continuing with the

supplementation of 2.0 milligrams per 2000 kilocalorie. During the final 77 days, a diet with approximately 0.3 milligrams per 2000 kilocalories was administered.

Range of Motion Measurements

Range of motion of all dexterity-related joints of the bilateral hands and wrists were measured at a consistent time and date each week. Measurements of the DIPs and PIPs were assessed with splints donned. Splints were doffed for the following measurements: wrist flexion, extension, ulnar deviation, radial deviation, MCP flexion, extension of all digits, and thumb IP flexion and extension. Refer to Appendix D for exact verbal cues and patient positioning. To assure intra-rater reliability throughout our case report range of motion measurements, the subject was measured twice and the average of the two measurements was recorded. “In hand goniometry, a plus or minus five degree margin of error is accepted even for experienced examiners adhering to standardized protocols.”²³ Therefore, if a change greater than five degrees from the previous week resulted, the measurement was re-assessed.

- Goniometric placement for wrist flexion and wrist extension includes the fulcrum placed at the ulnar styloid process, the stationary arm bisecting the forearm, and the moveable arm placed parallel to the 5th phalange. See Figures 1 and 2.

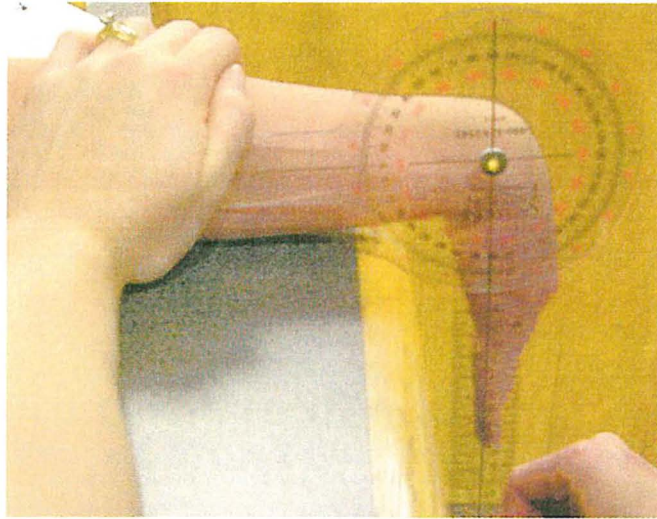


Figure 1. Goniometric Placement for Wrist Flexion.

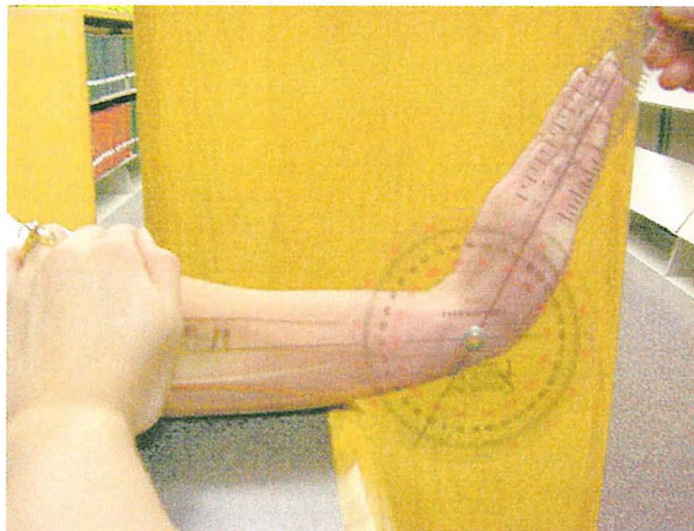


Figure 2. Goniometric Placement for Wrist Extension.

- Goniometric placement for ulnar and radial deviation includes placement of the fulcrum over the radiocarpal joint with the stationary arm bisecting the forearm and the moveable arm following the 3rd metacarpal. See Figures 3 and 4.

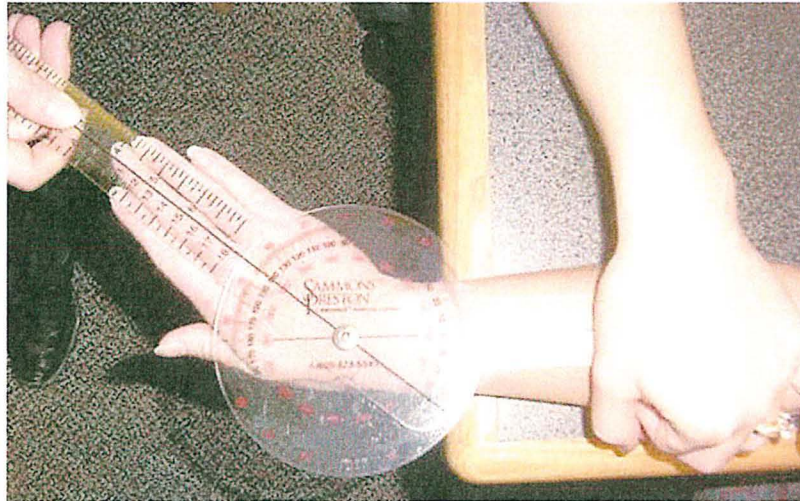


Figure 3. Goniometric Placement for Ulnar Deviation.

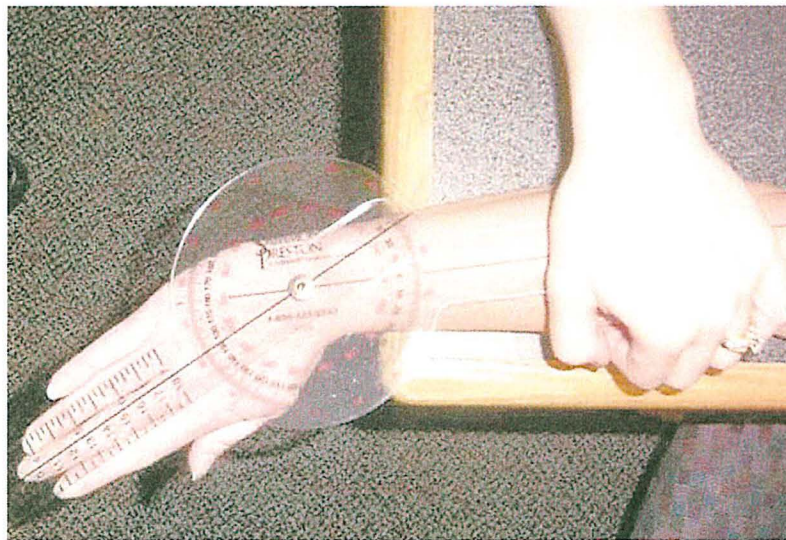


Figure 4. Goniometric Placement for Radial Deviation.

- Goniometric placement for the 1st digit IP flexion includes the fulcrum placed over the IP joint and the stationary and moveable arms parallel to the middle and distal phalanges respectively. See Figure 5.

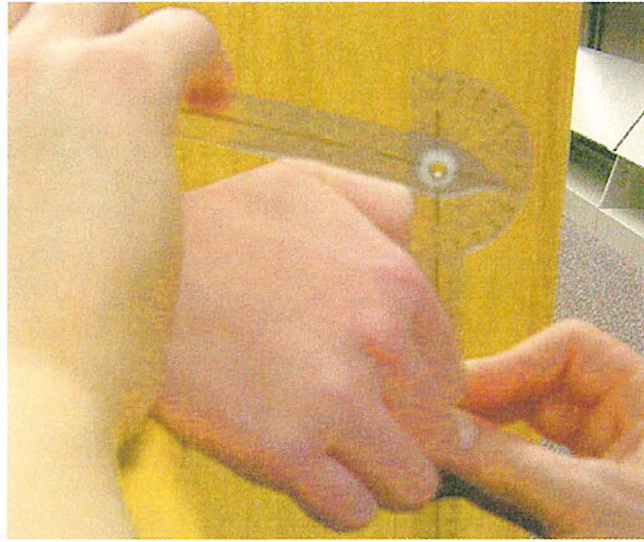


Figure 5. Goniometric Placement for 1st Digit IP Flexion.

- Goniometric placement for the 1st digit MCP flexion includes the fulcrum placed over the MCP joint and the stationary and moveable arms resting over the proximal and middle phalanges, respectively.

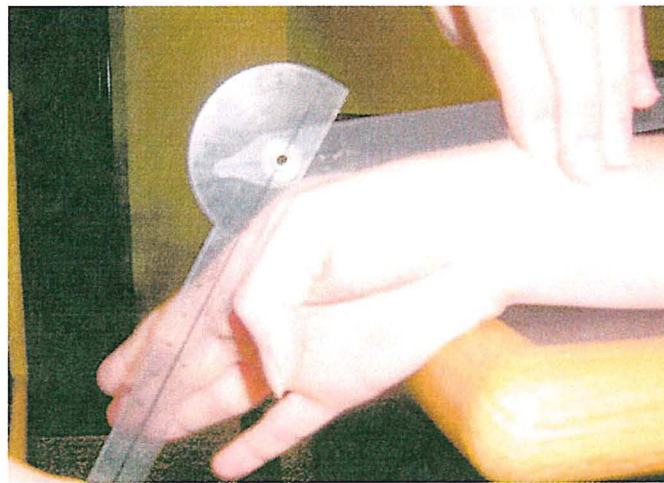


Figure 6. Goniometric Placement for 1st Digit MCP Flexion.

- Goniometric placement for flexion of the 2nd-5th MCP joints includes the fulcrum over the MCP joint and the stationary and moveable arms resting on the proximal and middle phalanges, respectively. See Figure 7.



Figure 7. Goniometric Placement for MCP Flexion.

- Goniometric placement for flexion of the 2nd-5th PIP joints includes the fulcrum placed over the PIP joint with the stationary and moveable arms resting on the proximal and middle phalanges, respectively. See Figure 8.

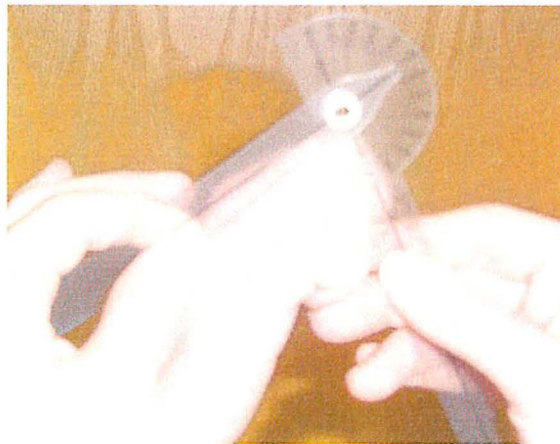


Figure 8. Goniometric Placement for PIP Flexion.

- Goniometric placement for flexion of the 2nd-5th DIP joints includes the fulcrum over the DIP joint and the stationary and moveable arms resting on the middle and distal phalanges, respectively. See Figure 9.



Figure 9. Goniometric Placement for DIP Flexion.

- Goniometric placement for extension of the 1st-5th MCP, PIP, and DIP joints includes the fulcrum over the respective joint, the stationary arm over the more proximal phalanx, and the moveable arm over the more distal phalanx.

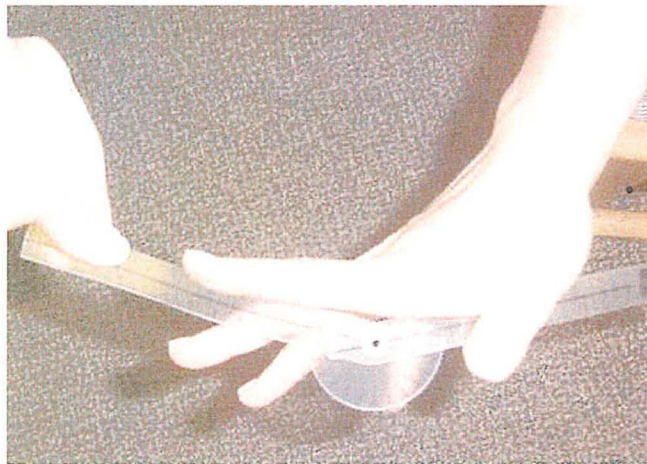


Figure 10. Goniometric Placement for Extension of the 2nd–5th Digits.

Poly-Arthritis Assessment

A Poly-Arthritis Assessment Form used in this study is located in Appendix E. This form included subjective and objective information regarding duration of morning stiffness (measured in hours), number of active joints, current joint pain, and fibromyalgic point totals.

The number of active joints was assessed by palpating the following joints bilaterally: The 1st-5th MCP, 1st IP, 2nd-5th PIPs and DIPs, radiocarpal, humeroulnar, glenohumeral, and sternoclavicular joints. They were rated subjectively by the patient in terms of pain and objectively by the tester in terms of boggiess. Pain was rated as minimal, moderate, and severe. Boggiess was measured in terms of present or absent. Even if the joint was subjectively sore, boggiess was the determining factor in labeling the joint as active.

Current joint pain was assessed using a visual analog scale rating pain from 0 to 10 (0 equaling no pain and 10 equaling worst possible pain). If the pain was rated between two numbers, it was recorded as "X.50". For example, if the subject reported her pain in between the numbers of five and six, 5.5 was recorded.

Fibromyalgic points were assessed in nine sites on the body, bilaterally. These included occipital, trapezius, supraspinatus, low neck, second rib, inner knee, outer elbow, gluteus, and trochanteric sites.

- The occipital point is located at the suboccipital muscle insertions.⁵
- The trapezius point is located in the midpoint of the upper trapezius musculature.
- The supraspinatus fibromyalgic point is located just superior to the scapular spine near the medial border.

- The gluteus fibromyalgic point is located in the upper outer quadrant of the gluteal muscle, in the anterior fold of the musculature.

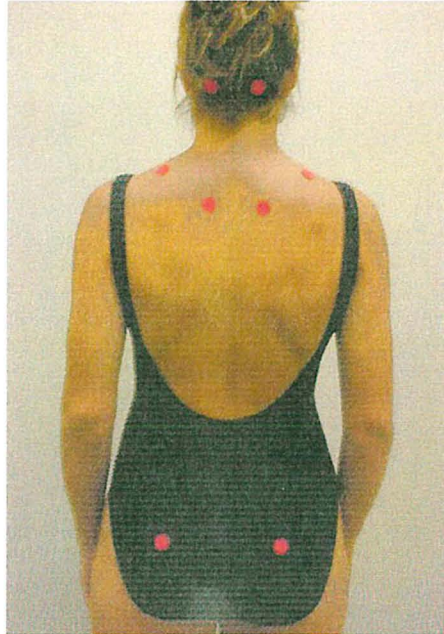


Figure 11. The Posterior Fibromyalgic Points Assessed.

- Deferring from the American College of Rheumatology defined points, the low neck fibromyalgic point⁴ is located in the 2nd intercostals space, just lateral to the costochondral junction, approximately one finger breadth.
- Also deferring from the American College of Rheumatology, the second rib point is located in the origin of the pectoralis major muscle, below the second rib in the intercostals space, near the costochondral junction.
- The fibromyalgic point tested at the outer elbow is located just distal to the lateral epicondyle by two centimeters.⁵



Figure 12. An Anterior View of the Upper Body Fibromyalgic Points Assessed.

- The inner knee point is located at the medial fat pad proximal to the joint line.



Figure 13. The Inner Knee Fibromyalgic Points Assessed.

- The trochanteric fibromyalgic point is located just posterior to the greater trochanter; it is found by having the patient internally and externally rotate the hip.
- Note the elbow and gluteus fibromyalgic points are also displayed in the lateral view.



Figure 14. The Lateral Fibromyalgic Points Assessed.

The patient was standing while the trochanter and gluteus fibromyalgic points were tested. All other points were assessed in the seated position. Approximately four kilograms of force was applied to the region in a circular fashion, covering a one-centimeter diameter. The patient rated the pain using a 0-2 scale; zero being no pain, one rating mild pain, and two equaling severe.⁴

Intra-rater Reliability and Inter-rater Reliability

Intra-rater reliability and inter-rater reliability was established for both testers prior to initiation of the testing procedures. Each tester measured nine subjects, using the average of three measurements. Measurements were recorded by an observer and were taken on two separate occasions, with a three-day span, to decrease the chance of rater biased or memory recall.

Joints	Rater One	Rater Two
1ST DIGIT-IP FLEXION	0.9710	0.9788
1ST DIGIT-IP EXTENSION	0.9741	0.9714
2ND DIGIT-MCP FLEXION	0.9044	0.9795
2ND DIGIT-MCP EXTENSION	0.9880	0.9964
3RD DIGIT-PIP FLEXION	0.9024	0.9192
3RD DIGIT-PIP EXTENSION	0.9295	0.9826
4TH DIGIT-DIP FLEXION	0.9767	0.9847
4TH DIGIT-DIP EXTENSION	0.9899	0.9231
WRIST FLEXION	0.9524	0.9620
WRIST EXTENSION	0.9489	0.9344
TOTAL DEVIATION	0.9011	0.9592

Table 1. Intra-Rater Reliability of Raters

Inter-rater reliability was established by having both raters measure the joints listed in the table below on nine subjects, using an average of two measurements for their final measurement. As with all measurements throughout this case report, if the average of two measurements fell between the two, the next highest whole number was used. The following is a table showing the inter-rater reliability using an Intraclass Correlation Coefficient (ICC). Literature states there is a substantial agreement of reliability if the average measure of ICC is equal to or greater than 0.90.²⁴ All of the following, except total deviation, met this requirement. Total deviation's ICC measure was 0.88 which, literature states is a high reliability.

Joint Motion Assessed	ICC
Wrist Flexion	0.98
Wrist Extension	0.94
Total Deviation	0.88
1st Digit DIP Flexion	0.97
2nd Digit PIP Flexion	0.90
3rd Digit DIP Flexion	0.95
5th Digit MCP Flexion	0.97

Table 2. Inter-Rater Reliability Between Raters

Data Analysis

Data was analyzed using the 10.0 version of SPSS statistical software for inter-rater and intra-rater reliability. All other data analysis was computed at the United States Department of Agriculture's Human Nutrition and Research Center in Grand Forks, North Dakota by a research analyst using the statistical program SAS, Version 8.02.

Reporting of Results

Upon completion of the study, a summary of the results will be completed and sent to Dr. Curtiss Hunt, M.D. at the United States Department of Agriculture's Human Nutrition and Research Center in Grand Forks, North Dakota. Copies of this case report will be given to both the preceptor, Beverly J. Johnson, PT, MS, and the University of North Dakota Health Sciences Library. This study was completed to partially fulfill the requirements for the University of North Dakota School of Medicine and Health Sciences Master of Physical Therapy Program.

Chapter IV

RESULTS

The data for this study was collected from the weekly range of motion measurements, Poly-Arthritis Assessment form, and self-assessment forms. The United States Department of Agriculture Human Nutrition and Research Center, Grand Forks, North Dakota provided data analysis for the case report. Limitations of analyzing the results must be noted because only one individual's records were used and this cannot be generalized towards the population of individuals with rheumatoid arthritis. Prior to the study, Dr. Curtiss Hunt, calculated a need for data from 14 individuals in order to establish a power of significance. See Appendix C.

Subject Profile

One female subject, age 49, participated in the study. She habitated at the Human Nutrition and Research Center in Grand Forks, North Dakota for the duration of the study. During this time, boron supplementation or deprivation was regulated by her daily food intake. Concurring with this alteration of her daily boron intake, the assessment of her joints was taken weekly. These assessments included range of motion of all dexterity-related joints of the hand and wrist, pain assessment, count of active fibromyalgic points, and active joint assessment. The subject was diagnosed with rheumatoid arthritis by meeting specific criteria listed in Appendix C.

Research Questions

Is the range of motion affected in dexterity-related joints through the administration of boron? Is there a significant reduction of the boggiess and/or sensitivity of the dexterity-related joints when a specified level of boron supplement is governed? Does the number of active fibromyalgic points chosen from the assessment form significantly alter when boron is administered in a specified dosage? What impact do the physical and psychological aspects have on the physical therapy treatment of these individuals?

Range of Motion

Range of motion was determined by using a two-point regression analysis. Those joints that demonstrated a $p < 0.05$ for boron supplementation, deprivation, or both are included in Table 3.

Soreness

Presented below is soreness as documented during the weekly Poly-Arthritis Assessment. The table shows the percentage of time the subject presented with soreness on boron supplementation compared to when the subject was deprived of boron. Joints that showed a difference of more than 25 percentage points are noted in Table 4.

Joint	Boron Supplementation	Boron Deprivation
Right 3rd MCP Flexion	X	
Right 5th PIP Flexion	X	
Left 5th PIP Flexion	X	
Right Wrist Extension	X	
Left 2nd MCP Extension		X
Right 2nd PIP Extension		X
Right Thumb MCP Flexion	X	X
Left Thumb IP Extension	X	X
Right 2nd MCP Extension	X	X
Right 2nd PIP Flexion	X	X
Left 2nd PIP Extension	X	X
Right 2nd DIP Extension	X	X
Left 3rd DIP Extension	X	X
Right 4th MCP Extension	X	X
Left 4th MCP Flexion	X	X
Right 5th MCP Flexion	X	X
Left 5th MCP Flexion	X	X
Left 5th PIP Flexion	X	X
Right Wrist Flexion	X	X
Right Total Wrist Deviation	X	X
Left Total Wrist Deviation	X	X

Table 3. Range of Motion Measurement Changes ($p < 0.05$)

Poly-Arthritis Assessment	% of Soreness With High Boron	% of Soreness with Low Boron
Left 3rd MCP	100.00	63.63
Left 2nd MCP	0.00	54.54
Right Glenohumeral	27.27	0.00
Right Radiocarpal	45.45	18.18
Right 3rd MCP	81.81	27.27
Right 2nd MCP	18.18	54.54
Right 1st MCP	9.09	45.45

Table 4. Soreness Present as Measured by the Poly-Arthritis Assessment Form

Bogginess

The Table 5 reports the resulting percentages that bogginess was noted by the rater during the weekly assessment.

Poly-Arthritis Assessment	% of Bogginess With High Boron	% of Bogginess with Low Boron
Left 2nd MCP	0.00	36.36
Right 2nd MCP	18.18	72.72
Right 1st MCP	100.00	54.54

Table 5. Bogginess Present as Measured by the Poly-Arthritis Assessment Form

Presence of Swollen Joints During Self-Assessment

The following table describes the frequency of swollen joints that were noted by the subject during her self-assessment. Only the joints displaying a difference of 15 points or greater are noted in the chart below.

Self-Assessed Joint	High Boron		Low Boron	
	Yes	No	Yes	No
R radiocarpal	29	48	59	17
R 5 th MCP	50	27	68	8
R 5 th DIP	48	29	74	2
R 4 th MCP	58	19	73	3
R 4 th PIP	60	17	75	1
R 4 th DIP	65	12	76	0
R 3 rd MCP	13	64	52	24
R 2 nd MCP	42	35	24	52
R 2 nd PIP	40	37	58	18
R CMC	9	68	58	18
R 1 st MCP	1	76	31	45
R 1 st IP	3	74	60	16
L radiocarpal	38	39	60	16
L 5 th MCP	40	37	71	5
L 5 th PIP	30	47	71	5
L 4 th MCP	64	13	76	0
L 3 rd MCP	25	52	54	22
L 2 nd PIP	46	31	61	15
L 2 nd DIP	50	27	69	7
L CMC	13	64	58	18

Table 6. Self-Assessment of Swollen Joints

Presence of Painful Joints During Self-Assessment

The table below indicates the joints shown to have a difference of 15 points or more in frequency from the subject's self-assessment data of painful joints.

Self-Assessed Joint	High Boron		Low Boron	
	Yes	No	Yes	No
R radiocarpal	5	72	57	19
R 5th MCP	20	57	70	6
R 5th PIP	26	51	70	6
R 5th DIP	48	29	74	2
R 4th MCP	60	17	73	3
R 4th PIP	59	18	75	1
R 4th DIP	65	12	76	0
R 3rd MCP	19	58	52	24
R 2nd MCP	43	34	25	51
R 2nd PIP	40	37	58	18
R CMC	8	69	58	18
R 1st MCP	2	75	35	41
R 1st IP	4	73	60	16
L radiocarpal	4	73	50	26
L 5th MCP	40	37	71	5
L 5th PIP	34	43	71	5
L 5th DIP	47	30	74	2
L 3rd MCP	31	46	54	22
L 2nd DIP	50	27	69	7
L CMC	7	70	58	18

Table 7. Self-Assessment of Painful Joints

Morning stiffness, while on boron supplementation, had a calculated mean of 0.909 hours, with a standard deviation of 1.375 as compared to 0.318 hours, with a standard deviation of 0.751, while deprived of boron. Pain averaged 4.273 on a 0-10 scale while on boron supplementation, with a standard deviation of 1.272. Pain averaged only 2.272 on a 0-10 scale while deprived of boron, with a standard deviation of 1.348. The total number of active joints was determined each week, presiding on the presence of

bogginess and soreness. This was calculated to have a mean of 5.364 joints while on supplementation of boron, as compared to 4.909 joints with deprivation of boron, with standard deviations of 2.767 and 2.844, respectively. Fibromyalgic points had a maximum of 36 points for the total count and the patient objectively presented with a mean of 15.182 while on boron supplementation, as compared to 9.909 while deprived of boron, with standard deviations of 4.665 and 3.833, respectively.

By analyzing the above information, it is apparent that boron supplementation resulted in a general overall decrease in the subject's average hours of morning stiffness, fibromyalgic tender points, and subjective pain; however, the active joints remained relatively consistent.

Chapter V

DISCUSSION

Rheumatoid arthritis is due to a systemic, inflammatory process chronically occurring within the human body. Joint and tendon destruction may be a debilitating result. Research has documented that boron supplementation has increased the range of motion of the joints in laboratory rats and delayed the onset of rheumatoid arthritis in rats.^{6, 7, 25} Pertaining to the former study, signs of inflammation and swelling were evident in the contralateral paw to a much greater degree with a boron low diet.²⁵ This suggests that ample amounts of boron may decrease the inflammation in joints of laboratory rats. No previous studies have documented these effects in human subjects at this time. The results of this case report were not consistent with those presented in the animal study.

Subjective pain, hours of morning stiffness, and fibromyalgic tender points decreased with the subject during high boron intake, however, range of motion was affected in roughly one-third of all motions tested in the dexterity-related joints. It is pertinent, to this scholarly project, that one does not generalize the effects of boron supplementation in dexterity-related joints to all individuals with rheumatoid arthritis. The information presented here is a case report for one subject only. No conclusive evidence can be made with these results, and the results should be looked at in their context only.

The results of this case report have shown that the number of active joints for our subject remained relatively constant. This demonstrates that the bogginess and soreness/sensitivity to palpation were still present. However, interestingly, the subjective rating of pain, fibromyalgic points, and hours of morning stiffness decreased with boron deprivation.

By analyzing the range of motion statistics, it was found that 21 motions out of the possible 64 motions tested displayed changes. These generally displayed slopes in a two-point regression analysis indicating an increase in the range of motion with boron supplementation and a decrease in the range of motion with boron deprivation in the measurements of dexterity-related joints for this subject with rheumatoid arthritis.

Limitations of Study

The first limiting factor of this study was the sample size of one. With only one subject used in this data analysis, generalization cannot occur. No conclusive evidence could be made due to the randomized effects with boron supplementation and deprivation.

Two raters were involved in the weekly assessments for this case report; however, further research may attempt to use only one rater. Literature supports intra-rater reliability as being higher than inter-rater reliability.²³

As rheumatoid arthritis and fibromyalgia are commonly inter-correlated, the tender points are a powerful discriminator against patients with rheumatoid arthritis and controls.⁵ For future studies, to increase the reliability and validity of assessing fibromyalgia points, raters should determine inter and intra-rater reliability to ensure the

use of approximately four kilograms of force using the pulp of the thumb or the first two or three digits.

Humans are highly complex individuals, and difficulty arises when attempting to compare human subjects with animal subjects. Even though a controlled environment existed, we are not able to control all factors.

The study was conducted in a region where seasonal changes occur. The study encompassed seasons from mid-winter through spring and into early summer. This may influence the joint inflammatory process. It is documented that persons with rheumatoid arthritis may have a high sensitivity to weather patterns, however one study indicated that this may not be clinically significant.²⁶ Individuals with fibromyalgic symptoms have reported aggravation due to environmental stress factors.^{27, 28}

Research supports that some psychological factors have an influence on the immune system²⁹ and, therefore, are an integral part of living with rheumatoid arthritis. Also, physical and emotional stress factors have proven to aggravate symptoms in individuals with fibromyalgia.^{27, 28} Further research may attempt to look more in-depth to the components of psychological self-assessment. During our data analysis of this study, we did not address the impact of psychological issues. The ability to cope with pain^{30, 31} and mood may all impact the subject's perception of pain and therefore, alter objective values of a study.

Physical Therapy Application

The above data represents the vast factors associated with rheumatoid arthritis and the impact it can have on the physical being of an individual. Physical therapists must

realize that psychological issues can result as the patient attempts to deal with the daily physical limitations of the disease. Physical therapy goals will focus on reducing pain, controlling inflammation, maintaining mobility, and minimizing stiffness, edema, and joint destruction.³ Physical therapy treatment for rheumatoid arthritis may include, but are not limited to the following: strengthening, stretching to improve or maintain range of motion, splinting to prevent deformity, biofeedback, TENS (transcutaneous electrical nerve stimulation), aerobic components, aquatic therapy, and gait analysis.

Strengthening is a large component of physical therapy. It is important to strengthen not only the hands or involved joints of an individual with rheumatoid arthritis, but it is also necessary to strengthen the other joints that may not yet be involved.³² Fernandez-Madrid³² states, "For example, some patients in whom the hands and other joints of the upper extremities are predominantly involved may not understand why they should exercise their legs." During exercise, the use of the legs helps with the efficiency of blood return to the heart and surrounding muscles.

Stretching exercises will most likely relieve the muscle tightness caused by either disuse or inactivity.³² One of the main purposes of stretching is to prevent contractures or to increase the range of motion after a contracture has occurred in individuals with rheumatoid arthritis. In progressive stages of rheumatoid arthritis, splinting can be a method of stretching scar tissue formed in the joint by providing a prolonged and gentle force to a specific joint or joints. Splinting can also be used during the inflammatory stage to rest the joints and maintain balance of the agonist and antagonist muscles.

It is important to realize that both strengthening and stretching should be

performed after the duration of morning stiffness has subsided, with the exception of the individual who's stiffness lasts all day.³² In the latter case, strengthening and stretching should not be performed when active joint involvement occurs, manifested by the evidence of inflammation and pain.

Electrical current therapies are a component often used in the realm of physical therapy treatments. Biofeedback has been reported to reduce the pain in individuals with rheumatoid arthritis.³³ TENS (transcutaneous electrical nerve stimulation) has been proven to reduce the painful symptoms associated with rheumatoid arthritis in 18 out of 20 individuals at the frequency of 70 hertz.³⁴

Dynamic exercise improves joint mobility, muscle strength, aerobic capacity and daily functioning in individuals with rheumatoid arthritis.¹⁶ Evidence in several studies does not support an adverse effect of exercise on joint integrity, or an increase in the inflammation of the joints.^{16, 35}

Due to the fact that swimming is a non-weight-bearing activity, it is ideal and beneficial for patients with rheumatoid arthritis because of the involvement of the joints in all extremities.³² Aquatic therapy is a non-impact activity and, therefore, results in a decreased amount of stress on the individual's joints.

When evaluating gait, dynamic exercises such as walking or jogging promote cardiovascular fitness, however, these exercises may not be possible or may even be contraindicated, depending on the individual's involvement.³²

Due to the chronicity of the disease process, patient education and establishing patient compliance to therapeutic treatment are essential to obtain maximal benefits. The

therapist must provide a balance between rest and activity to ensure that overexertion does not exacerbate the symptoms, but that the patient remains active enough to prevent deformity. Reducing the inflammatory process will allow the patient to be active and to decrease the likelihood of future joint destruction, especially in dexterity-related joints of the hand and wrist.⁴

Several items have been proposed and experimental in the hunt for a cure of rheumatoid arthritis. At best, palliative care has focused on a number of aspects including Cox-2 Inhibitors, massage, acupuncture, herbal remedies, and anti-inflammatories. One must realize as a physical therapist treating individuals with rheumatoid arthritis, that a multi-dimensional and holistic approach must be taken. As therapists, we can assure optimal treatment for our patients if we remain current on updated technology, treatment techniques, and potential cures for rheumatoid arthritis.

This case report must be interpreted with caution, due to the limitations of this study. Future research should address a sample size large enough to meet a statistical power that can be generalized to the population. As a sample size with statistical power would allow data analysis to determine a significant difference in collected data for boron deprivation and supplementation periods.

It is valuable to the integrity of the healthcare system and medical field as a whole, that further research be conducted on treatments for rheumatoid arthritis. The valuable information provided by research, combined with the physical therapy components, and patient relations with proper communication will allow for effective treatment of individuals with rheumatoid arthritis. Literature demonstrates aspects of

communication are positively correlated with patient satisfaction³⁶, adherence to treatments³⁷, and general health status³⁸. As healthcare providers, it is vital to listen to your patient, understand what he or she is saying both verbally and nonverbally, and combine all aspects of treatment and research with sincere care for your patients.

“People don't care what you know, until they know that you care.” ~Author Unknown

APPENDIX A

DEFINITIONS

1. Rheumatoid arthritis: is a progressive and systemic disease marked by inflammation, which leads to deterioration of the joints. Fibrosis of the synovium often results, causing a decrease in range of motion, stiffness, swelling, and possible deformity of the affected joints.³⁹
2. Bogginess: is a physical characteristic used to describe excessive fluid found in affected joints.
3. Fibromyalgia: is chronic and frequently difficult to manage pain in muscles and soft tissues surrounding joints that can be associated with rheumatoid arthritis.³⁹
4. Fibromyalgic tender points: characteristic “active” sites that are tender and can be distinguished from equally characteristic “control” points that are non-tender.⁴

APPENDIX B

OCT 03 2001

TOPIC PROPOSAL
UNIVERSITY OF NORTH DAKOTA
GRADUATE SCHOOL

Please Type

(Check One) Independent Study X Thesis _____ Dissertation _____ Project Design _____

Student Nicole Herda and Jessica Woehl

Date September 20th, 2001

Proposed Title A Case Report on the Range of Motion of Dexterity Related Joints in Patients with Rheumatoid Arthritis

Anticipated Graduation Date May, 2002

Nature of the problem/study, the procedure or methodology to be followed, and the anticipated results:

Rheumatoid arthritis is a progressive, destructive and chronic, inflammatory disease of the joint synovium. Signs and symptoms include pain, limited range of motion, swelling, and tenderness, which may progress to deformity. These manifestations may limit dexterity, independent living, and the overall well being of an individual. Living with daily restrictions proves to be a psychologically distressing experience.

An increase in the dietary boron level of laboratory rats has shown to have a positive effect on the range of motion in their involved joints. This concept was tested on a human subject at the United States Department of Agriculture's Human Nutrition Research Center in Grand Forks, North Dakota over a six-month period from January 9th to June 19th, 2001. Joint involvement was assessed using goniometric measurements, a Poly Arthritis form, along with palpation of 16 fibromyalgic points. The subject was measured on a consistent day and time each week. All external factors were kept constant within the whelm of our capabilities. Records were stored in a locked environment between uses. The study was conducted under the direction of Dr. Curtiss Hunt at the Human Nutrition Research Center and Beverly Johnson PT, MS at the University of North Dakota Department of Physical Therapy. Institutional Review Board approval was obtained, and inter-rater and intra-rater reliability were established prior to testing. A standardized verbal instruction regimen, to guide the subject and to encourage her to give her maximal effort during measurements, was used. We predict the increased intake of boron will have a significant influence on the range of motion in our subject.

The purpose of this case report is to analyze the effect of boron supplementation and to aid in improving the pathological related signs and symptoms of an individual with rheumatoid arthritis. The potential to decrease the clinical manifestations, and reduce the psychological stress of living with a chronic illness would benefit individuals with rheumatoid arthritis.

Signatures of approval as specified in the "Degree Requirements" section of the Graduate Bulletin.

Beverly Johnson PT, MS

ACTION Amr
Leah BT
DEAN OF THE GRADUATE SCHOOL
DATE 10/16/01

R1&2-06-P

EXPEDITED REVIEW REQUESTED UNDER ITEM _____ (NUMBER(S)) OF HHS REGULATIONS
EXEMPT REVIEW REQUESTED UNDER ITEM _____ (NUMBER(S)) OF HHS REGULATIONS

UNIVERSITY OF NORTH DAKOTA HUMAN SUBJECTS REVIEW FORM
FOR NEW PROJECTS OR PROCEDURAL REVISIONS TO APPROVED
PROJECTS INVOLVING HUMAN SUBJECTS

Please include ALL information and check ALL blanks that apply.

PRINCIPAL: Curtiss D. Hunt, Ph.D.,
INVESTIGATOR: Joseph B. Sleckman, MD, James G. Penland, Ph.D., Henry C. Lukaski, Ph.D. TELEPHONE: 701-795-8423 DATE: February 14, 2000
(Revised 5-22-00, Revised 11-15-00, 12-19-00, 10-3-01)
ADDRESS TO WHICH NOTICE OF APPROVAL SHOULD BE SENT: Emily Nielsen, PO Box 9034, Grand Forks, ND 58202-9034

SCHOOL/COLLEGE: USDA, ARS DEPARTMENT: GFHNRC PROPOSED PROJECT DATES: July 6, 2000- December 21, 2002
(Month/Day/Year)

PROJECT TITLE: Physiologic Amounts of Dietary Boron as a Factor in the Manifestation of Rheumatoid Arthritis (GFHNRC #143)

FUNDING AGENCIES (IF APPLICABLE):

TYPE OF PROJECT (Check ALL that apply):

☒ NEW PROJECT ☐ CONTINUATION ☐ RENEWAL ☐ DISSERTATION OR
THESIS RESEARCH ☐ STUDENT RESEARCH PROJECT
☒ CHANGE IN PROCEDURE FOR A PREVIOUSLY APPROVED PROJECT

DISSERTATION/THESIS ADVISER, OR STUDENT ADVISER:

PROPOSED PROJECT: ☐ INVOLVES NEW DRUGS (IND) ☐ INVOLVES NON-APPROVED
USE OF DRUG ☐ INVOLVES A
COOPERATING INSTITUTION

IF ANY OF YOUR SUBJECTS FALL IN ANY OF THE FOLLOWING CLASSIFICATIONS, PLEASE INDICATE THE CLASSIFICATION(S):

☐ MINORS (<18 YEARS) ☐ PREGNANT WOMEN ☐ MENTALLY DISABLED ☐ FETUSES ☐ PERSONS WITH
MENTAL RETARDATION
☐ PRISONERS ☐ ABORTUSES ☐ UND STUDENTS (<18 YEARS)

IF YOUR PROJECT INVOLVES ANY HUMAN TISSUE, BODY FLUIDS, PATHOLOGICAL SPECIMENS, DONATED ORGANS, FETAL
MATERIAL, OR PLACENTAL MATERIALS, CHECK HERE ☒

IF YOUR PROJECT HAS BEEN/WILL BE SUBMITTED TO ANOTHER INSTITUTIONAL REVIEW BOARD(S), PLEASE LIST NAME OF
BOARD(S):

Status: ☐ Submitted; Date ☐ Approved; Date ☐ Pending

1. ABSTRACT: (LIMIT TO 200 WORDS OR LESS AND INCLUDE JUSTIFICATION OR NECESSITY FOR USING HUMAN SUBJECTS).

Numerous findings from animal models show that low boron status is associated with several disorders including disturbances of normal fetal development, insulin release and exacerbation of rickets. In humans, it is associated with poorer attention and short-term memory, increased severity of osteoarthritis, and decreased circulating concentrations of 25-hydroxyvitamin D₃. The basis for these effects has not been clearly established. Recent studies with animal models have indicated that boron affects immune function; boron deprivation increased the severity and incidence of experimental rheumatoid arthritis, an inflammatory disease. Findings from these animal experiments support the hypothesis that physiologic amounts of dietary boron reduce the risk for inflammatory disease by serving as a suppressive signal that down-regulates enzymatic activities typically elevated during the normal inflammatory process such that boron permits elimination of pathogens but avoids autoimmunity. Previous studies in humans indicate that physiologic amounts of dietary boron improve mental function and vitamin D status but none have examined the physiologic role of boron on inflammatory disease. Although the findings with boron deficient animals are convincing, only controlled studies with human volunteers fed diets containing low (but common today) boron will establish whether such diets have important consequences for health in the general population.

PLEASE NOTE: Only information pertinent to your request to utilize human subjects in your project or activity should be included on this form. Where appropriate, attach sections from your proposal (if seeking outside funding).

2. **PROTOCOL:** (Describe procedures to which humans will be subjected. Use additional pages if necessary. Attach any surveys, tests, questionnaires, interview questions, examples of interview questions [if qualitative research], etc. the subjects will be asked to complete.)

Rationale and Objective: Several attempts have been made, including at the Grand Forks Human Nutrition Research Center, to establish that a dietary deprivation of boron results in changes in biochemical and physiological indices that could lead to pathological consequences. These studies have been particularly successful and most studies used animal models under nutritional stress including vitamin D, magnesium, or calcium deficiency. Variables typically examined here and at other independent laboratories were those related to bone and cartilage structure and function, energy substrate and mineral metabolism, immune function and embryological development. It is now well established that physiologic amounts of dietary boron help protect against moderate vitamin D deficiency (manifested as rickets) in animal models, that dietary boron improves circulating concentrations of vitamin D metabolites in humans and animals, and that boron is needed for normal embryological gastrulation of frog and fish species. There is further evidence from the fetal rat model that boron is important in vertebral column development. The exact molecular mechanism responsible for these effects has not been determined. However, in vitro interactions between boron and several boron-binding biomolecules are well characterized; boron is a reversible inhibitor of all examined serine protease and NAD^+ -, NADP -, and FAD -requiring oxidoreductase enzymes. Several of these enzymes are integral components of the neutrophil respiratory burst process, the blood coagulation cascade, or the complement and leukotriene biochemical pathways. These metabolic pathways are, in turn, major components of the normal inflammatory process, the physiological mechanism that normally eliminates antigens without evidence of clinically detectable inflammation.

Excessive inflammation leads to inflammatory disease. Findings from elsewhere indicate that rheumatoid factor is rapidly and completely precipitated in boric acid solutions (2%) in vitro and prompted the hypothesis that boron reacts with sugar moieties in the rheumatoid factor to form a reversible complex. Research in this laboratory on the possible relation between dietary boron and inflammatory disease was based on knowledge of the reversible nature of boron enzymatic inhibition and appreciation of rheumatoid arthritis as an inflammatory, autoimmune disease of unknown etiology. We demonstrated that physiologic amounts of dietary boron reduced paw swelling and increased circulating concentrations of natural killer cells in rats with antigen-induced rheumatoid arthritis. Thus, published research findings to present indicate beneficial immunomodulatory effects for dietary boron possibly brought about by the suppression, but not elimination, of the activity of enzymes involved in the normal inflammatory process. The proposed research will establish whether physiological amounts of dietary boron affect clinical manifestations of human rheumatoid arthritis, a chronic inflammatory disease more prevalent in single or divorced women compared to married women, and associated with lower income and lower educational levels. A study showed that the value of expected lifetime costs of rheumatoid arthritis, on a per capita basis, amounted to \$20,412 (1977 dollars). Careful assessment of mineral balance of volunteers with rheumatoid arthritis will substantially improve our ability to provide nutritional counseling to patients with rheumatoid arthritis.

Sample Size: A statistical power analysis was conducted to determine the number of subjects needed to achieve 90% power to detect significant ($\alpha=0.05$) treatment effects. Data from previous studies that had manipulated drug treatments for control of RA were used to estimate effect sizes and variance components. Based on the analysis of prior $\text{CD8}^+\text{CD25}^+$ lymphocyte concentrations, 14 subjects are needed to achieve 95% power. An analysis of tender or swollen joints indicated that 8 subjects are needed to achieve 99% power.

Participants: Fourteen, non-smoking (tobacco or medicinal marijuana), non-alcoholic women (with target of 60-65 years of age), with physician-diagnosed chronic rheumatoid arthritis (RA) (as described below), will be recruited by and Internet website (programmed so that the key words rheumatoid arthritis, bones, and boron will be found by search engines) or magazine or television advertisement throughout the United States. Letters soliciting referrals will be sent to physicians. The letter will explain the study and request that the physicians distribute the enclosed brochure to their patients. Patients who wish to participate can then call the HNRC toll free, write to HNRC, or contact them by e-mail. If direct solicitation to physicians is not productive, a letter with the same enclosed brochure will be sent to local chapters of the Arthritis foundation. Subjects selected to enter the study will be informed in detail of the nature of the research, including the risks and benefits.

Subjects may exhibit physical symptoms of RA in other than in the upper limbs or in extra-articular regions (within limits defined below) but must be fully ambulatory and able to carry out non-assisted bodily toilet, showering, and washing

functions (with modified toilet, shower, and sinks controls), collection (as described below) of all urine and fecal materials (with mechanical aids if needed), and consumption of all foods, beverages, nutrient supplements, and medications (with mechanical aids if needed). Candidates will be screened at no cost to them for medical, nutritional, and psychological health by telephone interviews, written questionnaires, report of their personal physician after local visit, examination of complete medical records by a study physician, and onsite examination by clinical laboratory, psychology, dietary, and medical staff and consultants. Medical records are obtained by asking the volunteer to fill out a release form to send to the clinic where their records are kept. Ineligible candidates and alternates will be notified by phone or mail. Alternates will be accepted if an original volunteer leaves or is dismissed from the study. women will be used because this faction of the population is most likely to have poor boron status and thus the findings can be directly related to this susceptible group.

Medical selection criteria:

A. Rheumatoid Arthritis (RA). At the time of selection, eligible candidates will manifest rheumatoid arthritis (RA) as defined by the American Rheumatism Association 1987 Revised Criteria for the Classification of Rheumatoid Arthritis (Arthritis and Rheumatism, 31:315-324, 1988). This is the presence of four or more of the following criteria:

- 1) morning stiffness in and around joints lasting at least one hour before maximal improvement;
- 2) at least three joint areas simultaneously have had soft tissue swelling or fluid (not bony overgrowth alone) observed by a physician. The 14 possible areas are right or left proximal interphalangeal, metacarpophalangeal, wrist, elbow, knee, ankle, and metatarsophalangeal joints;
- 3) at least one area swollen (as defined above) in a wrist, metacarpophalangeal, or proximal interphalangeal joint;
- 4) simultaneous involvement of the same joint areas (as defined in 2) on both sides of the body (bilateral involvement of proximal interphalangeals, metacarpophalangeals, and metatarsophalangeals is acceptable without absolute symmetry);
- 5) subcutaneous nodules, over bony prominences, or extensor surfaces, or in juxtaarticular regions, observed by a physician;
- 6) demonstration of abnormal amounts of serum rheumatoid factor by any method for which the result has been positive in <5% of normal control subjects; and
- 7) radiographic changes typical of rheumatoid arthritis on posteroanterior hand and wrist radiographs, which must include erosions or unequivocal bony decalcification localized in or most marked adjacent to the involved joints (osteoarthritis changes alone do not qualify).
- 8) Criteria 1 through 4 must have been present for at least 6 weeks.

B. Prior Manifestation of Rheumatoid Arthritic State: To limit the need for significant volunteer care, health status monitoring, and modification of existing facilities, all of the following additional selection criteria must also be met at time of selection:

- 1) RA status is stabilized as indicated in personal medical records;
- 2) No manifestation, for at least 2 years immediately prior of any inflammatory disease, other than RA, or chronic disease unassociated with rheumatoid arthritis;
- 3) Functional capacity is not Class 3: adequate to perform few or none of the duties of usual occupation or self-care;
- 4) Functional capacity is not Class 4: total or almost total incapacitation, with patient bedridden or confined to wheelchair, able to perform little or not self-care;
- 5) None of the following systemic manifestations of RA or adverse effects of drugs sometimes present in an advanced RA state are present:
 - a) Severe vasculitis manifest as necrotizing arteritis of either small- or medium-sized vessels, erythema elevatum diutinum (very painful, indurated crusted lesions) gangrene, intestinal infarction, myocardial infarction, central nervous system vasculitis, or renal vasculitis.
 - b) Felty's Syndrome (splenomegaly with neutropenia, hepatomegaly, lymphadenopathy, sinus infection, pneumonia, highly expressed rheumatoid arthritis, leg ulcers).
 - c) Eye
 1. Focal, diffuse, or nodular scleritis (congestion and inflammation of the sclera; deep aching, increased tearing; thinning of sclera [scleromalacia]; melting cornea syndrome [keratolysis]; nodular lesions that erode the sclera, with perforation of underlying ocular material [scleromalacia perforans/perforation of the eye]).

2. Eye movement disorders (rheumatoid nodules in tendons of ocular muscles; local cranial nerve palsy from vasculitis; cortical blindness from vasculitis).
3. Loss of epithelium over cornea in dry eye associated with Sjogren's syndrome.
- d) Compression neuropathy to cause:
 1. Bladder dysfunction
 2. Headache
 3. Cervical spine subluxation.
- e) Heart
 1. No prior history of heart failure, or hypertension
 2. Constrictive pericarditis and cardiac tamponade.
 3. Arrhythmias and conduction disturbances.
 4. Valvular abnormalities causing stenosis or insufficiency.
- f) Lung
 1. Caplan's syndrome (intrapulmonary nodules).
 2. Obstructive sleep apnea.
 3. Upper airway obstruction by cricoarytenoid arthritis.
 4. Pulmonary fibrosis.
- g) Gastrointestinal Tract/Liver
 1. Evidence of gastrointestinal ulcers or perforations as a result of RA medication or any other cause, lactose intolerance, malabsorption, inflammatory infiltrates of lamina propria, bowel infarction, postprandial abdominal angina, amyloid involvement in the gut, hepatitis, cholestasis, vasculitis;

Living Environment: The women will reside in the metabolic ward of the Grand Forks Human Nutrition Research Center. Each subject will be provided with a private bedroom with cable television, radio with wake-up alarm, intercom to 24-hour nurses station, and telephone, and a semi-private bathroom. Four separate lounges (for computer [with full Internet access], music, card game, big-screen TV, fireside, and other activities), one laundry room, one whirlpool bathroom, one craft room, one exercise (stationary bicycle) area, one ping-pong/active game area, one outdoor patio, one 24-hour nurses station, and one refreshment room (with refrigerator, sink, microwave) are adjacent to the private bedrooms. All meal consumption and several experimental assessments take place within the building on floors different than that of the main living suite that are accessible by either stair or an elevator. To avoid extraneous joint trauma and swelling, walking aids will not be provided except for movement in private bedroom and shared bathroom. Rather, in the unexpected situation where a subject experiences an RA flare-up that degrades ambulatory status, a non-motorized wheelchair escorted by a staff member will be provided until adequate ambulatory status returns. The subjects will consume only and all foods, beverages, and vitamin, mineral, or other supplements provided by the Grand Forks Human Nutrition Research Center and will be allowed to leave the immediate living or dining areas, or facility only when accompanied by a chaperone. Meal consumption is observed by specially trained dietary staff and irregularities are recorded. Subjects must agree to use only those personal care products and in the amounts approved by the principal investigator to limit and standardize extraneous chemical exposure.

Rheumatoid Arthritis Therapies: Specific therapies for RA prescribed by a physician or subject-selected prior to the start of the study are incorporated into the study design to standardize treatment and to reduce possible masking of the effects of dietary boron. As such, the approved therapies are continuations of previous therapies, not new treatments.

- A. **Methotrexate therapy for rheumatoid arthritis.** Active low-dose (7-20 mg/week) methotrexate therapy for rheumatoid arthritis is a selection criterion. The use of oral methotrexate in a low dose given once weekly has become the mainstay of therapy for active and sustained rheumatoid arthritis. All subjects must certify that they have received methotrexate for rheumatoid arthritis and rheumatoid arthritis therapy only as prescribed by a physician. All subjects must certify that the methotrexate therapy has been stable for at least the last 6 months before the start of the study. All subjects must agree to continue their individual methotrexate therapy throughout the study and only in the same form, brand, and dosage as that last prescribed by their personal physician before entry into the study.
- B. **Auxiliary therapies for rheumatoid arthritis.** Active auxiliary therapy for RA is not a selection criterion. However, four other specific auxiliary therapies for rheumatoid arthritis are permitted if they have been stable for at least 4 months before the start of the study. All subjects must agree to continue any approved pre-entry auxiliary therapy throughout the study and only in the same form, brand, and dosage as that taken before entry into the study. Any

subject not on one or more approved auxiliary therapies at the beginning of the study must agree to not start any auxiliary therapy during the study. The approved auxiliary therapies are:

1. Oral Nonacetylated salicylates (e.g., choline magnesium trisalicylate, magnesium salicylate [e.g., Magsal], sodium salicylate [Pabalate], salsalate or salicylsalicylic acid [e.g., Salflex, or Disalcid]. Acetylated salicylates [e.g., aspirin, Anacin Analgesic, Bufferin, Bufferin Arthritis Strength Analgesic Tablets]) ARE NOT permitted. Exceptions will be made at the discretion of the principal investigator.
 2. Oral Acetaminophen (e.g. Extra-Strength Tylenol),
 3. Oral Prednisone or equivalent and/or,
 4. Oral Hormone Replacement Therapy.
- C. Other therapy/medication for rheumatoid arthritis or other disease. During the study, the subjects must not regularly use medication except methotrexate for RA and the specific approved auxiliary therapies. Subjects must agree to complete avoidance of all other traditional therapies for RA and all nontraditional treatments for RA (including, but not limited to, acupuncture, massage, homeopathic medications, fish oil, dimethyl sulfoxide [DMSO], venom) during the study.
- D. Medication control. All approved therapy for RA or auxiliary RA therapy during the study will be supplied to the subjects at no cost to them. Subjects must agree that all storage, dispensing, and inventory tracking of all medications (prescribed and over-the-counter) are under the complete control of the staff nurses on duty in the metabolic ward and must agree to not keep any medication in their private possession. The frequency and dosage of any medication will be recorded.

Boron Content in Diet: Women aged 60-65 years are estimated to consume 0.731 mg of boron per day on average. For all women age 19 years and older, those in the 5th percentile are estimated to consume 0.35 mg boron per day; those in the 95th percentile, 1.95 mg boron per day. Upon entering the study, the women will be fed the basal diet containing approximately 2.0 mg per 2000 kcal for 14 days. For the second dietary period (77 days), one-half of the subjects will be maintained on this diet and the other half will be fed the basal, non supplemented diet so that it will supply approximately 0.3 mg per 2000 kcal. For the third dietary period (77 days), those subjects previously maintained on the basal diet will switch to the diet supplemented with boron (2.0 mg per 2000 kcal), and those subjects previously maintained on the basal diet with boron supplement will switch to the basal diet without boron supplement.

Experimental Diet: All subjects will be asked to not take dietary supplements for 30 days before study entry. Each subject will be asked to participate in the study for a total of 168 days. Body weight will be monitored but allowed to fluctuate because RA often causes muscle wasting. At weekly intervals, at the written request of the subject, and after subject consultation with the dietary staff, the number of calories in their diet may be adjusted either upward or downward in 200 calorie increments two weeks after the request is made. However, body weight loss will be limited to -2% of initial body weight and will be corrected with 200 calorie increment increases. Body weight gain is acceptable.

Mixed Western diets will be used such that the energy from protein, carbohydrate, and fat and all known essential nutrients the diet are similar to that consumed by women as estimated by a national food intake survey (U.S. Department of Agriculture Agricultural Research Service. *Data tables: food and nutrient intakes by individuals in the United States, by region, 1994-96. Table Set 13. Online.* ARS Food Surveys Research Group. February 1999). The calculated nutrient content of the diet will be adjusted by dietary supplements, if necessary to meet estimated average intakes of all known essential nutrients (except boron). To compensate for iron loss by phlebotomy, iron will be supplemented to provide about 27 mg per day. To compensate for known antagonistic effects of methotrexate on folic acid, folic acid will be supplemented at 1 mg above usual intake.

Cardiac Monitoring: Heart rhythm will be monitored by a 20-hour electrocardiogram obtained by ambulatory cardiography. These will be obtained every two weeks. Twelve lead electrocardiograms may be done to check unusual results.

Noninvasive RA Feature Assessment: To monitor and safeguard the health of the volunteer, physical assessments are conducted at three levels (volunteer, staff, and physician). All types of physical health assessment will be considered experimental variables. With written express permission of the volunteer, a copy or summary of the RA feature assessment findings will be sent directly to the volunteer's personal physician. To limit experimental bias, none of the members of the

research team, nursing staff, dietary staff, consulting or collaborating physicians, or any other staff at the Center, except for study physicians assigned to conduct physical examinations, are allowed to discuss, consult, or dispense advice concerning any medical treatment or medication related to RA. The same personnel are blinded to the dietary treatment.

A. Joint Function Assessment:

1. Daily: Self-reported checklist summaries morning stiffness and joint count. Staff assessment of swelling of proximal interphalangeal (PIP), metacarpophalangeal (MCP), and wrist joints, and subcutaneous nodules.
2. Weekly: Staff assessment of all limb, jaw, and clavicular joints identified on the standard Polyarthritis Assessment Form for swelling, damage, synovial effusion, tenderness, or stress pain; wrist, hand, finger joint range of motion by goniometry; hand and wrist volume by water displacement.
3. Biweekly: Staff assessment of grip strength.
4. Week 2 of first dietary period, weeks 6 and 11 of second and third dietary period: Staff assessment of manual dexterity by using the Purdue Pegboard procedure.

B. Extra-articular/Systemic RA Feature Assessment:

1. Daily: Self-reported checklist summaries of indications of night pain, fever sweats, malaise or weakness, dry eyes, dry mouth. Staff assessment of (but unlikely presence of) nailfold infarcts, epidermal ulcers, inflamed eyes, pleural pain, tenderness in spine between C7 and L4, Raynaud's phenomenon (spasm of the digital arteries with blanching and numbness of fingers), Sjogren's syndrome (dryness of mucous membranes and telangiectasias [dilation of terminal capillaries] or purpuric spots on the face).
2. Week 2 of first dietary period, weeks 6 and 11 of second and third dietary period: Study physician assessment of rheumatoid arthritic state by physical examination including monitoring for lymph node enlargement as a sign of methotrexate toxicity. Staff assessment of hand tremor by using a standard steadiness test procedure (ability to hold a stylus inside a series of holes of decreasing diameter without touching the sides of the hole).

Resting Energy Expenditure (REE): Weekly for first 3 weeks, then monthly thereafter: REE is elevated in RA and will be measured by indirect calorimetry which is a measure of the oxygen consumed and the carbon dioxide given out. The rate of O₂ consumption under resting conditions will be determined after a 12 hour fast. A face mask, similar to an oxygen face mask, will be used to collect respiratory gases after a 12 hour fast. Respiratory gases will be measured while the participants rest in a reclining position in a thermoneutral (room temperature) environment. At least 30 minutes will be allowed for stabilization of the respiratory gas measurements. Determination of O₂ consumption and CO₂ production will then be made for 15 minutes.

Venipuncture: All blood will be drawn after an overnight fast (usually 12 hours). Phlebotomy will be performed by medical technicians or registered nurses. Techniques will be those used in standard hospital and clinic settings. As summarized below, blood for health status indicators (maximum of 13 mL per phlebotomy) will be obtained during week two of the first dietary period, weeks 2, 4, 6, 8, 10, and 11 of the second dietary period, and weeks 2, 4, 6, 8, 10, and 11 of the third dietary period. Additional blood (maximum of 112 mL additional) for rheumatoid arthritis, inflammatory response, oxidative response and boron deficiency indicators will be obtained during week two of the first dietary period, weeks 6 and 11 of the second dietary period, and weeks 6 and 11 of the third dietary period. As described below (see Boron Metabolism Assessment by Stable Isotope Enrichment), additional blood will be drawn during week 8 of the second and third dietary periods (maximum of 24 mL each time). A maximum of 287 mL will be drawn in 8 weeks. The blood bank guidelines for blood donation volume and frequency is 475 mL every 8 weeks. The total maximum amount of blood drawn for the study is 712 mL.

Tests done with blood will emphasize variables that will determine whether boron supplementation affects inflammatory function, oxidative metabolism, and mineral metabolism. Tests will also be done to establish and monitor health status.

- 2
- A. Rheumatoid Arthritis Indicators: RBC sedimentation rate, rheumatoid factor, leukocyte phospholipase A₂, serum type II collagen, antibodies to type II collagen, plasma fatty acid profile, plasma pyridoxal-5'-phosphate, and zinc.
- B. Inflammatory Response Indicators: leukocyte subset populations, serum TNF-alpha, IL-1, IL-2, IL-6, granulocyte-macrophage colony stimulating factor (GM-CSF), insulin-like growth factor 1 (IGF-1), IFN-gamma, leukocyte TNF-alpha, dopamine, IL-8, and alpha-2 macroglobulin, C-reactive protein; leukocyte IL-1, IL-2, IL-6, granulocyte-macrophage colony stimulating factor (GM-CSF), IFN-gamma, phospholipase A₂; platelet phospholipase A₂.
- C. Oxidative Metabolism Indicators: leukocyte oxidative burst, erythrocyte copper-zinc superoxide dismutase, extracellular superoxide dismutase, leukocyte manganese superoxide dismutase, plasma ascorbic acid, glutathione, homocysteine, vitamin E, and erythrocyte protein carbonyl formation.
- D. Boron Deficiency Indicators: The following variables responded in previous human or animal model boron deprivation studies: protime/PTT, serum urea nitrogen, serum 25-hydroxyvitamin D₃, osteocalcin, glucose, triglycerides, insulin, ionized calcium, calcitonin, 17 beta-estradiol, testosterone, bone specific alkaline phosphatase, plasma and whole blood boron, magnesium, calcium, copper, and molybdenum.
- E. Bone Metabolism Indicators: PTH, IGF-I, IGF-IBP-1, IGF-IBP-3, IGF-IBP-4, Ionized Mg, and Under-carboxylated osteocalcin.
- F. Health Status Indicators: Erythrocyte sedimentation rate, complete blood count, folate, hemoglobin, hematocrit, ionized calcium, aspartate aminotransferase, alkaline phosphatase, albumin, serum phosphorus, iron, ferritin, total protein, creatine kinase, sodium, potassium, creatinine, total cholesterol.

Boron Metabolism Assessment by Stable Isotope Enrichment: Boron absorption and subsequent metabolism will be measured by using stable isotope enrichment technology. The typical natural ratio of the two stable (non-radioactive) isotopes of boron (B-10 and B-11) in foods is approximately 20:80 respectively. Volunteers will be provided a dose of B-10 that was incorporated naturally by hydroponically-grown broccoli plants. These B-10 enriched plants are harvested, freeze-dried, then fed to the volunteers during week 8 of the second and third dietary periods. An indwelling catheter is inserted into an arm vein for four hours to allow collection of 4 mL blood samples at 0, 0.5, 1, 2, 3, and 4 hours after the broccoli test meal is fed. Urine samples are collected at 0, 0.5, 1, 2, 3, 4, 5, 6, 7, 8, 12, and 24 hours, and days 2-10 after the test meal is fed. Daily fecal samples are collected between 0 and 10 days after the test meal is fed. Blood, urine and fecal samples are analyzed by mass spectroscopy to track the transient changes in the natural B-10:B-11 ratio that will occur after consumption of the B-10 enriched broccoli thus allowing calculations of boron absorption and metabolism.

Urine and Fecal Collection: Volunteers will collect all feces and urine so that the following tests can be done:

- A. Urine: Leukotriene panel, hydroxyproline, N-teleopeptide, urea, uric acid, creatinine, oxalate, nitrate+nitrite, aluminum, boron, calcium, copper, iron, magnesium, manganese, molybdenum, phosphorus, potassium, sodium, nitrogen, and zinc and urinary cAMP (nephrogenous aAMP).
- B. Feces: aluminum, boron, calcium, copper, iron, magnesium, manganese, molybdenum, phosphorus, potassium, sodium, zinc to allow determination of balance of these minerals; occult blood.

Brain Function (Electroencephalogram and Polysomnography): The methods and procedures described below have received approval from the University of North Dakota Institutional Review Board and the USDA Human Studies Committee for use in other studies performed at the GFHNRC.

- A. Awake State. Because published reports indicate that boron deprivation may affect brain electrophysiology (e.g., decrease tonic activation) and because experimentally-induced pain is reliably associated with changes in brain electrophysiology (e.g., increased delta frequency activity), the electrical activity of the brain while awake will be recorded by using standard electroencephalograph (EEG) techniques and procedures once during baseline and during weeks 6 and 10 of each dietary period for a total of three times during the study. A trained technician will fit the subject with a recording cap containing a standardized montage of electrodes to measure ongoing electrical activity at the scalp. Bipolar recording will be done by referencing scalp leads to an electrode attached with adhesive collar

and located over the mastoid bone behind the contralateral ear. A small amount of water-soluble glue will be applied to the scalp at each recording site to reduce impedance. The EEG will be recorded as the subject sits in a soundproof chamber located in the Psychology Laboratory and performs simple mental tasks (e.g., subtraction by 7's, visual and auditory vigilance) or relaxes during eyes open and eyes closed periods. Visual tasks will be presented on a monitor and auditory tasks will be presented through stereo speakers. Overt responses will be registered by pressing buttons located on the arm of the subject's chair. While in the EEG recording chamber, the subject is observed by a technician on a closed-circuit television system and communicates with the technician via a two-way intercom system. EEG recording sessions require approximately 45 minutes to complete.

- B. Sleep State. Because changes in brain activation in response to dietary boron supplementation may be even more apparent during sleep than when awake, and because decreases in tonic nervous system arousal may affect sleep quality or quantity, brain electrical activity during sleep will be assessed once during baseline and during week 10 of each dietary period for a total of three times during the study. The electrical activity of the brain during sleep will be recorded by using standard polysomnographic [EEG, electrooculogram (EOG), electromyogram (EMG), and respiration] techniques and procedures. A total of 10 electrodes will be applied by a trained technician - two electrodes with a water-soluble gel to the scalp for EEG, two electrodes with adhesive collars near the outer canthi of both eyes for EOG, two electrodes with adhesive collars over the submentalis muscle of the chin and one electrode with an adhesive collar over the anterior tibialis of each leg for EMG, and one electrode with an adhesive collar over each mastoid as references. All of the above electrodes will be of the silver-silver chloride type. In addition, an oral-nasal thermocouple and a strain gauge placed around the chest just over the breasts will be used to monitor respiration. Following electrode application, the subject will go to bed and all electrodes will be connected through a single multi-conductor cable to an amplifier located at the head of the bed. The subject will be then allowed to sleep normally and will be free of visual monitoring throughout the night. Electrodes will be removed by a member of the nursing staff when the subject awakens in the morning. Room conditions will permit the subject to call a nurse at any time during the night if the subject needs to get out of bed (bathroom trips, etc.). To acclimate the subject to wearing electrodes during sleep, the subject will be fitted and will sleep with all electrodes one night prior to the first recording night. Therefore, the subject will actually participate in the polysomnography procedure a total of seven nights during the study, however, recording of subject electrophysiology during sleep will not exceed a total of six nights over the course of the entire study. The evening before and the morning after PSG, subjects complete a brief Sleep Behavior Inventory to record their mood and sleep quality and related characteristics (5 min)

Psychological and Behavioral Function: The methods and procedures described below have received approval from the University of North Dakota Institutional Review Board and the USDA Human Studies Committee for use in other studies performed at the GFHNRC. Based on the hypothesis that dietary boron influences central nervous system arousal, it is likely that boron supplementation will affect performance and behavior. Therefore, sensory-motor and spatial skills, cognitive processes and mood states will be assessed. The forms listed below are commercially available and/or copyrighted tests with use restricted to qualified professionals. They will be provided to the IRB upon request.

- A. Sensory-motor and spatial skills (e.g., eye-hand coordination) and cognitive processes (e.g., attention, memory and reasoning): Psychomotor and cognitive function will be assessed by using standardized tasks designed for "normal" populations and administered on a personal computer three times, once during each of the three dietary periods. Test sessions require approximately 60 minutes and will be performed under the guidance of a trained technician in a testing cubicle located in the Psychology laboratory at the Grand Forks Human Nutrition Research Center. Based on previous studies of other minerals, assessment of function in the following areas will be done, with the corresponding computer task(s) in parentheses: sensory-motor integration (visual pursuit), motor fatigue (tapping), planning and spatial orientation (two- and three-dimensional pattern matching), attention (continuous vigilance), perception (object search, visual density comparison, color-word identification), encoding and working memory (symbol-digit), long-term memory (object and pattern recognition), and reasoning (object classification). Subjects will be monitored by a trained technician while they perform the tasks to ensure compliance with task instructions and protocol. Not all tasks may be administered to all subjects due to time constraints.
- B. Mood states (e.g., anxiety, depression, hostility, vigor): Mood states will be assessed during the first dietary period and during weeks 6 and 10 of each of the second and third dietary periods for a total of five times during the study by using standardized paper-and-pencil tests designed to assess mood states in a normal population. These tests are purchased from commercial test publishers and administered in a group setting by a trained technician or psychology

graduate student in accordance with all standards established for test administration, interpretation and confidentiality by the American Psychological Association. Test sessions are conducted in a comfortable, quiet room located in the metabolic unit. Tests are untimed and typically require from 10 to 20 minutes to complete; thus, a test session lasts about 60 minutes. Based on previous studies of boron, administration of the following tests will be done: Multiple Affect Adjective Checklist, Spielberger State-Trait Anxiety Inventory, State-Trait Depression Adjective Checklist, Center for Epidemiology Study-Depression, Beck Depression Inventory and Spielberger State-Trait Anger Inventory.

- C. Historical and current pain, pain attitudes and daily activities. History of pain will be assessed with the McGill Pain Questionnaire during recruitment. Weekly, subjects will complete the 10 minute Multidimensional Health Assessment questionnaire. Daily throughout the study, subjects will report the location, intensity, aversiveness and duration of pain by using visual analog scales. Use of medications to provide pain relief will be recorded and analyzed.
- D. Sleep, intellectual and social functioning, verbal and auditory memory, and handedness assessments: made by the Psychology Laboratory staff members to facilitate the interpretation of data and to monitor subject psychosocial adjustment during participation in this long-term, live-in study and collected at the beginning of the study. Also at that time, the Lateral Preference Schedule will be administered to determine handedness and other aspects of dominance. Level of intellectual functioning will be determined by the 90-minute Multidimensional Aptitude Battery that will be administered to subjects as a group one time during the first month of the study. Once during the second and third dietary period, verbal and auditory memory will be measured with the 45-minute Memory Assessment Scale and social functioning will be determined by the 45-minute Interpersonal Behavior Survey. In addition, the 90-minute Minnesota Multiphasic Personality Inventory will be administered during subject recruitment and at the conclusion of the study.

Activity Monitoring: Gross behavioral activity will be monitored continuously throughout the study by having subjects wear an Actiwatch (Mini Mitter, Sunriver, OR) that contains an accelerometer capable of sensing motion with a minimal resistance force. The Actiwatch will be worn above the wrist bone on either hand and secured by either a plastic or elastic band, at the subject's discretion.

Vision and Auditory Function: To ensure that subject scores on tasks administered during awake EEGs and performance testing are not confounded by preexisting deficits in sensory function, vision and hearing will be assessed by using standard screening equipment and procedures during the first two weeks of the study. Binocular and monocular acuity, color vision, and stereo depth perception will be determined by using a Titmus Vision Tester, and one-ear and two-ear hearing abilities (air conduction only) will be determined by using a Beltone Audiometer. These tests require approximately 30 minutes and will be administered by a trained technician in a comfortable, quiet room located in the Psychology Laboratory at the Grand Forks Human Nutrition Research Center.

Body Composition: Body composition measurements will be used to assess the relationship of boron metabolism to body size and to lean body mass in women. Thus, at regular intervals throughout the study, body composition will be determined by dual energy x-ray absorptiometry (soft tissue composition and bone mass), whole-body scintillation counting using a uniform isotope source (fat-free body mass), anthropometry (height, weight, skinfold thickness, and circumference), and bioelectrical impedance (lean body mass). These methods or procedures are described below and have received approval from the University of North Dakota Institutional Review Board and the USDA Human Studies Committee for use in other studies performed at the GFHNRC. All of these procedures will be done at the Grand Forks Human Nutrition Research Center by experienced, specially trained staff members. In addition, the test administrator of the dual x-ray absorptiometry scan has been trained by Hologic, Inc. staff and is an USDA Radiation Safety Committee approved radiation user.

A. Soft tissue composition and bone mass.

- 1. Dual X-Ray Absorptiometry- This test will be performed to aid in the estimation of total muscle mass. The whole-body measurement will be made by briefly exposing each volunteer to collimated low-level x-rays. These measurements will provide information about soft tissue composition (fat and fat-free, bone-free) of the whole body. The volunteer lies supine on a bed that moves over a tungsten stationary anode x-ray tube, pulsed alternatively at 70 and 140 Kvp and operated at a tube current of 2 milliamps peaks. The effective beam energies are 43 and 110 keV. The total time for a whole-body scan is less than 16 minutes. The whole body scan will be performed three times during the study. The radiation dose for each whole-body scan is 4.0 microSievert (μSv) or 0.4 millirem (mrem) for

a total of 1.2 millirem. The DXA is calibrated on the day of scheduled testing by scanning a spine phantom which contains a known amount of bone mineral (hydroxyapatite). Limits of agreement are $\pm 1.5\%$ of certified values. If data are outside of this tolerance, a representative from the manufacturer is contacted for service to the DXA. Volunteer scans are postponed until the DXA has been repaired.

2. Whole-Body Scintillation Counting Using a Uniform Isotope Source (UNIS) - Potassium-40 is a naturally occurring radioisotope of potassium exclusively found in the fat-free body (muscles, bone and organs). External counting of potassium-40 permits an estimation of changes in fat-free body mass. Three times during the study, the volunteer will lay supine on a mattress above and below which are suspended sodium iodide crystals used to count gamma ray emissions from the body's natural burden of potassium-40. Because each volunteer's body size and shape may change with the boron dietary treatments, it is necessary to correct the measured counts of gamma ray emissions due to potassium-40 decay by exposing the volunteer to a uniform isotope source before each whole-body count to determine the body's burden of potassium-40. A sodium-22 (a radioactive form of sodium) source will be placed under the mattress for a one-minute count while the volunteer lies on the mattress. This procedure, which exposes the volunteer to a radiation dose of much less than 0.01 microsevert (0.001 millirem), is necessary to obtain absolute measures of total body potassium that are independent of changes in body geometry. The total radiation dose for 3 repetitions of this procedure is less than 0.03 microsevert (0.003 mrem). This test permits an assessment of changes in body cell mass during the boron-low and boron-adequate dietary periods.

B. Anthropometry - This test is performed three times during the study to aid in the estimation of body composition and body physique. Standing height or stature and body weight will be determined. Measurements of skinfold thickness at triceps, biceps, subscapular, midaxillary, calf, mid-anterior thigh, juxta-umbilical and iliac sites; bichondylar diameters and circumferences at the wrist, humerus and femur, calf, thigh, waist, hips, upper and lower arm will be made twice during the study.

C. Bioelectrical Impedance - Measurements are made for validation of this technique to predict body composition and fluid distribution. Whole-body and regional impedance variables will be determined three times during the study during the study with a single- (50 kHz; RJL Systems; Mt. Clemens, MI) and again with multi-frequency (1kHz to 1 MHz; XITRON; San Diego, CA) impedance device. This measurement is made with the volunteer supine on a non-conductive table with the arms and legs abducted from the body and the fingers extended. Small, adhesive electrodes are placed on the hands and feet, upper and lower arm, and thigh for whole-body and regional or limb measurements. A constant current source introduces a safe, painless, non perceptible, radiofrequency, alternating current of 100 microamps at frequencies ranging from 1 kilohertz to 1 megahertz into the distally-positioned electrodes on the hand and foot and the voltage drop is measured at the proximally-placed electrodes.

Both single- and multiple frequency instruments are calibrated with an approved equivalent circuit (calibrator) consisting of precision resistors and capacitors. The instruments are calibrated before each test of a volunteer. Tolerance is within 1% certified values of resistance, reactance or impedance. If measurements on the calibrator exceed 1%, the device is returned to the manufacturer for repair. Volunteers undergo bioelectrical impedance measurements only after the devices have been restored to correct operation.

Health Status Surveillance: If, during the course of the study, a health variable moves out of the normal range, the subject and the test results will be sent to a Center-selected physician at no cost to the subject.

Adverse Reactions or Health Problems: Adverse reactions are unlikely, and but could include problems such as food intolerance, faintness with blood draws, or common health care problems unrelated to the research, such as infectious illnesses, muscle strain, physical injuries, or previously unrecognized health problems. Each situation will be handled individually, with all relevant information discussed with the volunteer. The volunteer may be advised to consult with a physician, at the expense of the research center if related to the research, or at their own expense if unrelated to the research. For physician consultations initiated by the Center, transportation within a 100-mile radius of the Center will be paid for by the Center. If a volunteer insists on a visit outside of those limits, they will most likely be dismissed from the study. No health-related information will be provided to a health care center without the express written consent of the volunteer. If the problem interferes with the research, or if the volunteer no longer meets the research criteria of being generally healthy, then the volunteer will be dismissed from the study. If the problem does not interfere with the research, then continuation will be at the volunteer's discretion. Temporary variances in procedures (e.g. missed or delayed meals or testing) may be

allowed if they do not interfere with the main objective of the research, but the volunteer will not be pressured to remain in the study.

Emergency Response: The Altru Health System's ambulance (located 1 mile away) will be called for emergency medical care. The Grand Forks police and/or fire department will be called as needed. First aid supplies, fire extinguishers and fire blankets are available. Full-time staff includes a CPR-certified nurse staffing the Metabolic Unit around the clock, a physician who is certified in Advance Cardiac Life Support, and a chemical safety officer. Policies and procedures for Emergency Response (including fire, bomb threats, and tornado) are in place for the Center.

Premature Dismissal Criteria: Subjects found to willfully and/or significantly disregard any rule or guideline mandated by the study or unilaterally elect, for any reason, to end involvement in the study prior to natural termination of the study will be dismissed at the earliest convenience of the Center and at no physical jeopardy to the subject with full forfeiture of unearned per diem. If the Center determines that continued involvement in the study might be harmful to the physical or mental state of a subject or if development of an illness or a condition might affect the research results, the subject will be dismissed at the earliest convenience of the Center and at no physical jeopardy to the subject with full forfeiture of unearned per diem.

3. BENEFITS: (Describe the benefits to the individual or society.)

Direct benefits include the satisfaction from participating in a worthwhile research study that will benefit humanity because it will advance knowledge about the importance of boron for health and well being, especially as it relates to the control of rheumatoid arthritis. Information may be used to plan better diets or to change the dietary recommendations for boron. In appreciation for the participation of the volunteer, she will receive \$35 per day to be paid every two weeks. The total amount of the honorarium that the volunteer will receive if they complete the study will be \$5,880.

4. **RISKS:** (Describe the risks to the subject and precautions that will be taken to minimize them. The concept of risk goes beyond physical risk and includes risks to the subject's dignity and self-respect, as well as psychological, emotional, or behavioral risk. If data are collected which could prove harmful or embarrassing to the subject if associated with him or her, then describe the methods to be used to insure the confidentiality of data obtained, debriefing procedures, storage of data for the required three years, final disposition of data, etc.)

Living Environment: Group living on the Metabolic Unit and following the study procedures will result in appreciable loss of freedom and privacy. Their life will be much more regimented. They will lose much of their individual choices because the diet, many living conditions (such as meal times, waking time, sharing a bathroom, and escorts when off the Unit), procedures, and activities are decided by the study protocol and unit rules.

Rheumatoid Arthritis Therapies: All obligatory RA therapies during the study are those prescribed by a physician or volunteer-selected prior to entry into the study. As such, the therapies are a continuation of previous therapies, not new treatments.

Rheumatoid Arthritis (RA) Flare: In the unlikely case of an RA flare, strategies to ameliorate the flare will supercede requirements of any research objective. All relevant information will be discussed with the volunteer. Each case involving an RA flare will be handled individually. If a flare-up occurs, the volunteer will be seen by a physician to ensure that the condition is treated. With the volunteer's permission, all data will be sent the volunteer's primary physician, in their hometown, as soon as it becomes available and that physician will be continually updated on the volunteer's state.

Boron Content in Diet: Boron deprivation impairs reproduction of lower vertebrates, exacerbates the rachitic state, and increases the severity of experimental rheumatoid arthritis in an animal model. In humans, boron deprivation reduces vitamin D metabolite serum concentrations, decreases brain electrical activity similar to that observed in nonspecific malnutrition, decreases performance in tasks of motor speed and dexterity, attention and short-term memory. There is no Recommended Daily Allowance for boron because the requirement for boron has not been determined. Past studies with postmenopausal women at this Center indicate that it is not difficult to achieve a reduction in blood boron concentrations. However, symptomatic human boron deficiency has not been defined and severe or marked indications of boron deficiency were not noted in any previous metabolic study with volunteers. Findings from animal model systems indicate that any human boron deficiency symptom will be more pronounced when there are concurrently nutritional or physiological stressors. In conjunction with a magnesium-low intake (109 mg/d), a daily boron intake of 0.36, compared to 3.23 mg per day (comparable to that in a diet with fruits, vegetables, and legumes), decreased systolic and diastolic blood pressure but within the physiological range, and lengthened the QRS complex.

Experimental Diets: Every effort has been made to provide palatable diets acceptable to most people. However, some subjects are likely to become tired of consuming the same limited number of foods every third day for 168 days. Although the experimental diets will provide less food variety than the average U.S. diet, they will otherwise be no more likely to result in nutrient deficiency or dietary risk than the typical U.S. diets. The calculated nutrient content of the diet will be adjusted by dietary supplements if necessary to meet average intakes of all known essential nutrients (except boron) as estimated by a national food intake survey.

Cardiac Monitoring: There are no known risks associated with ambulatory cardiogram monitoring and 12-lead EKGs. However, some individuals may experience skin irritation from the electrode placement. If skin irritation occurs, various skin care measures will be used and alternate sites used. To protect the volunteer from possible harm, significant Holter electrocardiographic (ECG) changes will be cause for stopping boron depletion and starting boron repletion. The ECG changes considered significant include: 1) For the volunteer who initially has 0 or 1 ventricular premature discharge (VPD) during the first two Holters, an increase to 5 VPDs per 20 hours will be considered an aggravation. 2) For the volunteer who has 2 or more VPDs during the first two Holters, an aggravation has occurred when there is a four-fold increase in VPDs or a ten-fold increase in repetitive forms. 3) The appearance of rhythm abnormalities not present during the first two Holters such as atrial fibrillation, AV block and tachycardia. Confirmation of rhythm changes will be by a second Holter ECG done after detecting the changes for the first time and will be investigated by use of a 12-lead ECG.

Noninvasive Joint Function Assessment: The Purdue Pegboard procedure is expected to cause transient pain but similar to that associated with typical daily activities involving fine motor skills. The normal end-feel during range of motion assessments of normal joints is either hard, firm, or soft depending on respective bone-bone contact, tension of ligaments, or compression of muscle bulk. In assessment of RA-affected joints, motion in the appropriate plane to reach end-feel is terminated at the first sign of subject discomfort.

Resting Energy Expenditure (REE): There are no known risks associated with this procedure. The participants may experience some minor discomfort with the equipment used to collect respiratory gases.

Venipuncture: There may be some discomfort as the needle enters the skin, but this lasts only a few seconds. About 10% of the time a small bruise may develop at the needle site, but this resolves in two weeks or less. Less than 0.1% of the time the site may become infected, but this is easily treated with antibiotics. One hundred twelve (112) mL will be drawn five times, 13 mL will be drawn 8 other times, and 24 mL will be drawn two other times for a total of 712 mL or about 1.5 pints over 24 weeks. A maximum of 287 mL of blood will be taken within an eight-week period. This is considerably less than blood bank donation limits of 475 mL every eight weeks and is needed to ensure that the anemia sometimes associated with rheumatoid arthritis does not strengthen if present. The normal range of hemoglobin for females ages 18–49 years is 12.0–16.0 mg/dL. Slight anemia (≤ 10 g of hemoglobin/dL) is often present during the initial diagnosis of rheumatoid arthritis. However, hemoglobin concentrations were 12.7 ± 0.6 mg/dL in both classes (either receiving or not receiving methotrexate) of male and female subjects with inflammatory arthritis in a study reported in 1996. To prevent possible anemia from strengthening or from developing, the iron content of the diet has been elevated to about 25 mg/day. Nonetheless, the iron status of the subjects will be monitored. The blood volume withdrawn will be reduced to that needed for determination of health status if 1) an initial hemoglobin of ≥ 10 mg/dL falls below 10 mg/dL or 2) an initial hemoglobin of ≤ 10 mg/dL falls $> 10\%$ of the initial value. If this does not alleviate the anemic state, the subject will be evaluated by a local physician and given supplemental iron as prescribed.

Boron Stable Isotope Administration: There are no known risks associated with consumption of a natural boron isotope via incorporation into broccoli other than possible transient intestinal gas and bloating associated with broccoli consumption per se. The presence of an indwelling catheter for 4 hours will cause some distress and is similar to that used by clinics for a glucose tolerance test.

Urine and Fecal Collection: There are no known risks associated with these procedures. There may be odor from the urine and fecal collection. This can be minimized by keeping the samples cool in the refrigerator provided for this purpose in the volunteer's bathroom.

Brain Function (Electroencephalography and Polysomnography): There are no known risks associated with electroencephalography or the collection of other electrophysiologic data related to polysomnography as proposed. However, some individuals may experience mild, transient discomfort during electrode placement on or removal from the scalp, face, neck and legs.

Psychological and Behavioral Function: There are no known risks or discomforts associated with the assessment of sensory-motor and spatial skills, cognitive processes, motor tremor or mood states. If there are any concerns regarding psychological and behavioral assessments the subject may discuss these with the psychologist or psychology research assistants (supervised by a licensed clinical psychologist), with whom she will be meeting on a regular basis.

Activity Monitoring: There are no known risks or discomforts associated with activity monitoring.

Vision and Auditory Function: There are no known risks or discomforts associated with the vision or hearing tests.

Psychology Debriefing Procedure: During the last week of the study, the Research Psychologist and other psychology staff will meet with each research subject individually, and in groups when appropriate, to present to her all available performance, psychological and electrophysiological data collected on her, to provide interpretation of results when appropriate, and to receive feedback concerning all testing done by the Psychology Laboratory. Care will be exercised to stress individuality in performance and the fact that comparisons are within rather than between subjects. Therefore, presentation of normative data will rarely be done. Experience with this debriefing process indicates that subjects greatly appreciate this discussion of their data and leave the study satisfied in knowing what data was collected and why, and how they performed on the various tests and tasks administered throughout the study.

Body Composition:

- A. Soft tissue composition and bone mass.

1. Dual X-Ray Absorptiometry: The total radiation dose in this procedure is less than 1.5 mrem. This is approximately 15% of the radiation exposure incurred during a chest X-ray. It is equivalent to spending 8 hours in a jet airplane at a cruising altitude of 25,000 feet or spending approximately 1.5 weeks in the Colorado plateau area. The procedure will be performed three times and results each time in exposure of less than 0.5 mrem. Average annual radiation exposure in the United States is 360 millirem per person. The lowest dose estimated to provide good analytical precision has been calculated for use in the study. Two concerns about radiation exposure are that it can cause cancer or shorten life. A report (BEIR V, 1990) summarizing the effects of radiation, based mainly on survivors in Japan of World War II atomic bombs at Hiroshima and Nagasaki, has indicated that an acute total body dose of 10,000 mrem would cause approximately 800 excess cancer deaths and 14,500 years of life lost per 100,000 persons. If the effect of radiation at high doses is assumed to be proportional to the effect at low doses, the 1.5 mrem dose received in this study could result in 0.125 "extra" cancer deaths per 100,000 people and reduce life span by an average of 11.5 minutes per person. However, it is impossible to accurately estimate the excess deaths because a 1.5 mrem dose is an insignificant exposure when compared to the lifetime exposure of about 24,000 mrem from natural sources such as cosmic rays and radon.
 2. Whole-Body Scintillation Counting Using a Uniform Isotope Source (UNIS): The radiation dose in this procedure (0.001 mrem) is extremely low, approximately 700 times less than the daily radiation exposure from natural background radiation sources (0.7 mrem).
- B. Anthropometry - There are no known risks involved in the anthropometric and skinfold thickness measurements. However, some individuals may experience transient, minor discomfort during the measurement of skinfold thickness.
- C. Bioelectrical Impedance - There are no known risks associated with this procedure.

Confidentiality of Data Handling: To reduce the risk of losing privacy of personal information, confidentiality will be stressed with all staff members involved. Each volunteer will be assigned an identification number that is used to anonymously identify data. Staff will enter collected data into a password-coded computer system using only the volunteer identification number. All the consents, personal information, and medical data will be kept in a locked file at the Grand Forks Human Nutrition Research Center for at least three years after completion of the study. Access will be limited to approved staff members. Upon disposal, any paper that contains names and/or personal information will be shredded.

5. **CONSENT FORM:** Attach a copy of the **CONSENT FORM** to be signed by the subject (if applicable) and/or any statement to be read to the subject. If no **CONSENT FORM** is to be used, document the procedures to be used to assure that infringement upon the subject's rights will not occur.

Describe where signed consent forms will be kept for the required 3 years, including plans for final disposition or destruction.

A copy of the consent form is attached. The informed consent is distributed when a small (approximately 30) contingency of prospective volunteers are brought to Grand forks for an on-site visit. The prospective volunteers take the consent form home and those selected to participate in the study bring the form with them when they return to Grand Forks. The form is signed the day they enter the study. Signed consent forms and data will be kept at the Grand Forks Human Nutrition Research Center in a locked file for at least three years after completion of the study. Our current policy is to keep all consent forms indefinitely. If future technology facilitates another secure medium for storage of these forms, paper copies will be shredded.

6. For **FULL IRB REVIEW** forward a signed original and fifteen (15) copies of this completed form, including fifteen (15) copies of the proposed consent form, questionnaires, examples of interview questions, etc. and any supporting documentation to the address below. An original and 19 copies are required for clinical medical projects. In cases where the proposed work is part of a proposal to a potential funding source, one copy of the completed proposal to the funding agency should be attached to the completed Human Subjects Review Form if the proposal is non-clinical; 7 copies if the proposal is clinical medical.

Office of Research & Program Development
University of North Dakota
Grand Forks, North Dakota 58202-7134

On campus, mail to: Office of Research & Program Development, Box 7134, or drop it off at Room 105 Twamley Hall.

For **EXEMPT** or **EXPEDITED REVIEW** forward a signed original, including a copy of the consent form, questionnaires, examples of interview questions, etc. and any supporting documentation to one of the addresses above. In cases where the proposed work is part of a proposal to a potential funding source, one copy of the completed proposal to the funding agency should be attached to the completed Human Subjects Review Form.

The policies and procedures on Use of Human Subjects of the University of North Dakota apply to all activities involving use of Human Subjects performed by personnel conducting such activities under the auspices of the University. No activities are to be initiated without prior review and approval as prescribed by the University's policies and procedures governing the use of human subjects.

SIGNATURES:

Principal Investigator		Date
Project Director or Student Adviser		Date
Training or Center Grant Director		Date

INFORMED CONSENT STATEMENT

TITLE: Physiologic Amounts of Dietary Boron as a Factor in the
Manifestation of Rheumatoid Arthritis
Study 143 Written 2-11-00, Revised 5-22-00, 11-15-00, 10-3-01

INVESTIGATORS: Curtiss D. Hunt, Ph.D., Joseph B. Sleckman, MD, James G. Penland,
Ph.D., Henry C. Lukaski, Ph.D.

INSTITUTION: UNITED STATES DEPARTMENT OF AGRICULTURE,
AGRICULTURAL RESEARCH SERVICE
GRAND FORKS HUMAN NUTRITION RESEARCH CENTER
Box 9034, 2420 2nd Ave. N.
Grand Forks, ND 58202
Phone 701-795-8353 or 1-800-562-4032

This is an important form. Please read it carefully. It tells you what you need to know about this study. If you agree to take part in this research study you need to sign the form. Your signature means that you have been told about the study and what the risks are. Your signature on this form also means that you want to take part in this study.

Am I Eligible for this Study?

You are invited to participate in this research study designed to establish that dietary boron is important in alleviating the symptoms of rheumatoid arthritis. We are extending this invitation because:

- 1) You are a woman who does not smoke and are not an alcoholic..
- 2) You have active, but stabilized, rheumatoid arthritis as certified by your personal physician.
- 3) You do not show advanced indications of rheumatoid arthritis.
- 4) You are taking methotrexate for rheumatoid arthritis and rheumatoid arthritis therapy only as prescribed by a physician.
- 5) The dosage of methotrexate has been stable over the last 4 months before the start of the study.

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- 6) The only additional therapies that you currently take for your rheumatoid arthritis (if at all) besides methotrexate are:
- a) nonacetylated salicylates (like Disalcid) for pain or swelling. Exceptions will be made at the discretion of the principal investigator.
 - b) acetaminophen (like Tylenol)
 - c) prednisone or its equivalent,
 - d) hormone replacement therapy (like Premarin)
 - e) or some combination of one or more of these therapies.
- 7) The dosages of the additional therapies has been stable over the last 4 months before the start of the study.
- 8) You ceased taking acetylated salicylates (like aspirin) four weeks before the start of the study for relief of inflammation and pain,
- 9) You are in good mental health,
- 10) You are fully able to walk around unassisted and are able to carry out non-assisted bodily toilet, showering, and washing functions, collection of all urine and stool materials (as described below), and consumption of all foods, beverages, nutrient supplements, and medications,
- 11) You have no chronic condition or illness other than rheumatoid arthritis.

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Why is this Study being Done?

Boron is a mineral that plants need for life. It is also necessary for the reproduction of frogs and fish. In chicks with rickets (vitamin D deficiency), boron makes their bones grow straighter. In rats with a form of rheumatoid arthritis, boron reduces swelling in the paw. For women, there is no recommended dietary boron allowance although their daily intake of boron is estimated to be 0.73 milligram per day. A milligram is a measure of weight far smaller than an ounce; two poppy seeds weigh a milligram. Postmenopausal women ingesting 0.36 milligram of boron per day are prone to net boron loss as determined by a balance study. Balance is the measurement of boron taken in minus the amount excreted in the urine and feces; this value should be slightly positive during growth and near zero when body size and composition is being maintained.

The study that you have agreed to participate in will establish whether normal amounts of boron in the diet changes your symptoms of rheumatoid arthritis. By measuring whether you lose or keep much more of a mineral than you take in, we will be able to substantially improve our ability to provide nutritional counseling to patients with rheumatoid arthritis.

How Long will I be in the Study?

The study lasts for 168 days (24 weeks).

What are the Living Conditions?

Except for periodic visits to a physician, the study will be carried out at the Grand Forks Human Nutrition Research Center (GFHNRC) which has a metabolic unit that will accommodate 14 volunteers for long-term, live-in studies. You will have a private bedroom with cable television, intercom to a nursing station, a radio, a telephone, and a semi-private bathroom.

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In case you experience a rheumatoid arthritis flare-up that affects your ability to walk, you will have access to a walking aid for use and staff assistance in your room or bathroom, but only a non-motorized wheelchair escorted by a staff member outside of those areas.

We will give you a list of personal care items (like toothpaste) that are acceptable by us for you to use. In your free time, you may leave the Center only when accompanied by a chaperone provided by the Center. Priority will be given to scheduled meals and tests. Your cooperation and attention to the rules and regulations governing your conduct on the Metabolic Unit are expected. A nurse will be present on the metabolic unit 24 hours a day and a physician and psychologist will be on call for any problems (medical or otherwise) which may arise.

What Medications Can I take?

All rheumatoid arthritis treatments approved by us are provided to you at no cost and are stored, dispensed, and inventoried by nurse on duty. All medications must be consumed in the presence of the nurse. You agree to take only those treatments for rheumatoid arthritis that we approve. These are the following:

Treatment	Agreement	Agree (check if you agree)
Oral Methotrexate	You certify that you took oral methotrexate for rheumatoid arthritis and for rheumatoid arthritis only as prescribed by a physician for at least one year before the start of the study.	
	You certify that the dose of methotrexate has been constant for at least the last 6 months before the beginning of the study.	
	You agree to keep taking the same brand, form, and dosage of methotrexate as you were last prescribed by your physician before entry into the study.	

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<p><u>Oral Prednisone (or equivalent)</u></p> <p>Like: Deltasone Prednicen-M Sterapred</p>	<p>If you took prednisone (or equivalent) before the beginning of the study, you agree to keep taking the same brand, form, and dosage of prednisone (or equivalent) as you were last prescribed by your physician before entry into the study EXCEPT during a rheumatoid arthritis flare-up certified and treated by a physician.</p> <hr/> <p>If you DID NOT take prednisone (or equivalent) before the beginning of the study, you agree to NOT start taking prednisone or equivalent at any time during the study EXCEPT during a physician-certified rheumatoid arthritis flare-up.</p>	
<p><u>Oral Nonacetylated Salicylates</u></p> <p>Like: Disalcid, choline magnesium trisalicylate, Magsal, Pabalate, salsalate or Salflex</p>	<p>If you took nonacetylated salicylates (like Disalcid) or other drugs for pain and swelling approved by the principal investigator before the beginning of the study, you agree to keep taking the same brand, form, and dosage of these therapies for rheumatoid arthritis as you were taking before entry into the study EXCEPT during a rheumatoid arthritis flare-up certified and treated by a physician.</p> <hr/> <p>If you DID NOT take these drugs before the beginning of the study, you agree to NOT start taking nonacetylated salicylates at any time during the study EXCEPT during a rheumatoid arthritis flare-up certified and treated by a physician.</p>	
<p><u>Oral Acetaminophen</u></p> <p>Like: Anacin-3, Extra-Strength Tylenol</p>	<p>If you took acetaminophen (like Tylenol) before the beginning of the study, you agree to keep taking the same brand, form, and dosage of approved acetaminophen as you were taking right before entry into the study EXCEPT during a rheumatoid arthritis flare-up certified and treated by a physician.</p> <hr/> <p>If you DID NOT take acetaminophen (like Tylenol) before the beginning of the study, you agree to NOT start at any time during the study EXCEPT during a rheumatoid arthritis flare-up certified and treated by a physician.</p>	

I have read this page and agree with the content _____

Hormone Replacement Therapy	<p>You certify that, if you take hormone replacement therapy, it was started and held constant for at least 4 months before the beginning of the study.</p> <hr/> <p>If you took hormone replacement therapy (like Premarin) before the beginning of the study, you agree to keep taking the same brand, form, and dosage of hormone replacement as you were taking right before entry into the study EXCEPT during a rheumatoid arthritis flare-up certified and treated by a physician.</p> <hr/> <p>You agree NOT to start hormone replacement therapy after the study has started.</p>	
Other therapies for Rheumatoid Arthritis	<p>You agree NOT to continue nor start any other traditional or non-traditional therapy or treatment for rheumatoid arthritis other than the drug listed in this table after the study has started EXCEPT during a rheumatoid arthritis flare-up certified and treated by a physician.</p>	

What Will I Eat?

- A. A three-day menu rotation. During the course of the study, you will be fed a diet made from common foods and ingredients that can be bought at a regular grocery store. The diet will contain all known nutrients necessary for life in the amounts similar to that consumed by women (except for boron for part of the time) as estimated by a national food intake survey. The diet will be served on a three-day menu rotation for 168 days. Women 60-65 years old are estimated to consume 0.73 milligrams of boron daily. At the beginning of the study, you will be fed the diet containing 2.0 milligram of boron per 2000 calories per day for 14 days. For the next 77 days, you will, by random selection, either remain on this boron supplemented diet (2.0 milligram of boron per 2000 calories) or go to the boron non-supplemented diet so that your boron intake will be about 0.3 milligram of boron daily.

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For the final 77 days, you will switch to which ever diet you did not consume during the previous 77 days. You will be expected to consume only and completely the food, drink, and mineral or vitamin supplements provided by the GFHNRC dietary staff.

- B. Food intake/calories adjustments. At your written request, and after consultation with the dietary staff, the number of calories in your diet may be adjusted either upward or downward in 200 calorie increments two weeks after the request was made. However, body weight loss will be limited to -2% of initial body weight and will be corrected by 200 calorie increment increases. Body weight gain is acceptable. Your body weight will be measured regularly.
- C. A broccoli test meal. Twice during the study after an overnight fast, you will consume a quantity of warm, cooked broccoli that has been grown in a mineral water solution. The broccoli contains mainly just one normal kind of the mineral boron instead of the usual two so that we can determine how fast boron is taken up by the body and then excreted. **What**

Will Happen in the Study?

Cardiac Monitoring: Your blood pressure, pulse, and temperature will be taken regularly. On a regular basis throughout the study, your heart beat will be monitored for 20 hours by an electrocardiogram (ECG or EKG) by using a heart beat recorder. This machine, worn as a belt, is a small tape recorder that records the electrical activity of your heart for 20 hours through foam adhesive electrodes temporarily attached to your chest. You will be free to move around and to go off the metabolic unit while wearing this machine. Twelve-lead resting electrocardiograms may also be done. This takes about 15 minutes, lying on a cot with electrodes on your chest.

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Noninvasive RA Feature Assessment: On a daily basis, you will self-record the degree of morning stiffness and the location of all joints that are swollen or painful. On a daily basis you will fill out a questionnaire that asks whether you are experiencing night pain, fever sweats, weakness, dry eyes, or dry mouth. On a daily basis, the staff will examine your hands and wrists for swollen joints and nodules under the skin. The staff member will determine the volume of each hand by placing each in a graduated cylinder filled with water. To monitor the status of your rheumatoid arthritis, the staff will examine you, on a daily basis, for nailfold blood vessel clotting, skin ulcers, inflamed eyes, hand redness, red spots on the face. At the same time, they will ask you whether you have any chest pain, tenderness in the spine, or dry mouth.

Each week, the staff will inspect all limb, jaw, and upper chest joints on your body for evidence of swelling, tenderness, stress pain, and damage, and will test all wrist, hand, finger, and thumb joints for range of movement. Every other week, the staff will test your grip strength by having you squeeze a rolled blood pressure cuff.

Five times during the study, you will 1) visit a physician who will conduct a physical examination to monitor your rheumatoid arthritic state, 2) place small pegs in a pegboard for assessment of manual dexterity, 3) hold a stylus inside a series of holes of decreasing diameter without touching the sides of the hole.

Resting Energy Expenditure: Once during the first three weeks, then monthly thereafter, your lung gases will be measured before you eat in the morning while you rest in a reclining position and after you have let your body rest for 30 minutes. You will breathe through a face mask, similar to an oxygen mask, while the lung gases are being collected and measured.

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Blood Draws:

A. Regular blood draws. Blood will be taken from a vein in your arm 13 different weeks so that the amount of various minerals, vitamins, and other important substances it contains can be measured. Some of these measurements will be used to assure that no harm to your health is occurring; others will tell if boron is of practical nutritional importance for rheumatoid arthritics. Trained technicians or registered nurses use standard needles and syringes similar to those used in hospitals and clinics to obtain blood. A 13 milliliter (0.9 tablespoons) sample will be drawn 8 of the 13 times and an 112 milliliter (7.5 tablespoons) sample will be drawn 5 of the 13 times over 24 weeks. All blood will be drawn after an overnight fast (usually 12 hours) and before breakfast.

B. Measuring boron movement through the body. Twice during the study, we will determine how fast boron is absorbed and moves through your body into the urine after it is eaten as a special broccoli test meal (discussed below). A needle will be inserted into a vein in your arm and taped in place for 4 hours. This will be done in the morning before breakfast after you have fasted overnight. The needle in your vein will be kept open with normal saline solution between blood draws and before each blood draw a small amount (1.5 mL) of blood which contains saline will be discarded. This does not cause any discomfort beyond that of needle or catheter insertion and is the same procedure used in hospitals. You will be given a serving of broccoli prepared as described below (see Boron Stable Isotope Administration). Blood samples of 2.5 milliliter (0.2 tablespoon) will be withdrawn through the

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infusion set in your arm before you are given the broccoli serving and at five intervals afterwards for a period of four hours. A total of 24 milliliter (1.6 tablespoons) will be taken for each of the 2 tests. Four hours after completion you can eat the next regular meal.

- C. Total blood volume. The total amount of blood taken during the entire study is for a total of 712 milliliter or about 1.5 pints. A maximum of 287 milliliter (0.6 pints) of blood could be taken within an eight-week period. This is less than the blood bank donation limits of 475 milliliters (1 pint) every eight weeks.

Boron Stable Isotope Administration: You will be expected to eat a serving of broccoli twice during the study. The broccoli was grown in a greenhouse in a water solution with all the normal nutrients for growth. The broccoli was given only one kind of natural boron. After you eat the broccoli, the natural boron will be absorbed and will pass through the blood stream before it is excreted in the urine. You will be asked to void at 0, 0.5, 1, 2, 3, 4, 5, 6, 7, 8, 12, and 24 hours. The blood (described above under Blood Draws; Measurement of Boron Movement Through the Body), urine and stool samples are analyzed for boron to determine how fast the boron was absorbed, then excreted in the urine.

Urine and Stool Collection: You will be expected to collect all your stool and urine throughout the study in bags and containers provided by the Center. These will be analyzed to determine the excretion of important minerals, including boron, magnesium, and calcium, that may be affected by the dietary manipulations.

Brain Function (Electroencephalogram and Polysomnography): The electrical activity of your brain while awake will be recorded three times during the study by using an

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electroencephalogram (EEG). A trained technician from the Psychology Laboratory will fit you with a cap resembling a swimmer's cap, which contains numerous electrodes (sensors) designed to measure ongoing electrical activity at the surface of your scalp. A reference electrode will be attached on the bone behind each ear using an adhesive collar and a small amount of conductive gel will be applied to your scalp to help with recording. While your EEG is being recorded, you will sit in a sound-proof chamber and either relax or perform simple mental tasks (for example, counting by 7's, watching a television screen for a certain letter to appear, listening to a series of tones for a certain sequence to occur). While in the EEG recording chamber, you will be observed on a closed-circuit television system and may communicate with the technician at any time via a two-way intercom system. The EEG recording session will require about 45 minutes.

Three times during the study, for two consecutive nights each, you will have your brain's electrical activity recorded while you sleep. Your eye movements, muscle tension, and respiration will be monitored simultaneously. This procedure, called polysomnography (PSG), is a simple one. Electrodes (sensors) will be attached to several locations on your scalp, face, neck, and legs. Also, an elastic band sensor will be placed around your chest to measure breathing. All electrodes will be attached by using a non-irritating adhesive and a small amount of conductive gel will be applied to each electrode to help with recording. A trained technician will apply the electrodes, you will go to bed, and the electrodes will be connected to a small box at the head of your bed. For the remainder of the night, you will be allowed to sleep as you normally would, undisturbed and without observation. Should you need to get up during the night (for example, have to go to the bathroom), you can call the nurse over your intercom and the nurse will come to your room to disconnect your electrodes from the box. The electrodes will be

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removed by a nurse when you first awaken the next morning. To familiarize you with the recording procedure, you will sleep with all electrodes on one night prior to the first recording night. Therefore, counting the six recording nights, you will participate in the PSG procedure a total of 7 nights during the course of the entire study.

Psychological and Behavioral Function: A variety of psychological and behavioral assessments will be done on a regular basis throughout the study. Sensory-motor and spatial skills (for example, eye-hand coordination) and cognitive processes (for example, attention, perception, and memory) will be tested three times during the study by having you perform simple tasks on a personal computer. Examples of tasks include tapping a key on the keyboard, using a computer mouse to track an object moving across the computer screen, searching a group of common objects for two of a kind, memorizing and recognizing lists of words or simple geometric patterns, and categorizing objects. Test sessions require about 60 minutes and are performed under the guidance of a trained technician in a testing cubicle located in the Psychology Laboratory at the GFHNRC. Following completion of the computerized tasks, we will assess motor tremor by measuring hand steadiness; this brief procedure requires about 10 minutes. You will also complete the brief (about 5 minutes) Multiple Affect Adjective Checklist.

Other psychological assessments will be made by having you complete paper-and-pencil questionnaires. Weekly throughout the study, you will complete the Multi-Dimensional Health Assessment Questionnaire, a measure of arthritis-related pain, fatigue, helplessness and global health; this questionnaire requires about 10 minutes. Five times during the study, you will complete the State-Trait Anxiety Inventory, State-Trait Depression Adjective Checklist, Center

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for Epidemiological Studies Depression Scale, Beck Depression Inventory and State-Trait Anger Inventory; total time to complete all five questionnaires will be about 60 minutes. Three times during the study, you will have your verbal and auditory memory evaluated with the Memory Assessment Scale; this evaluation will require about 45 minutes. Once at the beginning of the study, you will complete a sleep history and a questionnaire about hand and eye dominance. Later in the study, you will also be administered an intelligence test (Multidimensional Aptitude Battery), and measures of personality (Minnesota Multiphasic Personality Inventory) and sociability (Interpersonal Behavior Survey). These tests each require about 45-90 minutes to complete and help us better interpret other data collected from you. All psychological and behavioral tests will be administered by a trained technician in accordance with standards established for test administration, interpretation, and confidentiality by the American Psychological Association. All paper-and-pencil testing is conducted in a comfortable, quiet room located in the metabolic unit or in the Psychology Laboratory at the GFHNRC.

During the last week of the study, the research psychologist and other psychology staff will meet with you individually, and in groups when appropriate, to present all available performance, psychological and electrophysiological data collected from you, to provide interpretation of your results when appropriate, and to get your thoughts about the testing done by the psychology staff.

Activity Monitoring: Your daily activity will be measured continuously throughout the study by having you wear an activity watch (accelerometer) that counts body movements. You may wear the watch above the wrist bone on your dominant or non-dominant hand, with a plastic or elastic band, whichever you chose.

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Vision and Auditory Function: During the first two weeks of the study, your vision and hearing will be tested by using standard screening equipment and procedures similar to those used in testing vision for a driver's license and for testing hearing in elementary school children. These tests require about 30 minutes and are administered by a trained technician in a comfortable, quiet room located in the Psychology Laboratory at the GFHNRC.

Dual X-Ray Absorptiometry: This test is used to assess and describe your body composition. Whole body composition is an outcome variable that will be measured during the study. Three times during the study, you will go to a laboratory where you will lie on your back on a bed that will move over an x-ray source for 20 minutes. One scan of your body from head to foot will be performed. For this test you will wear loose fitting clothing that does not contain metal.

Whole-Body Scintillation Counting Using a Uniform Isotope Source (UNIS): This test is also used to assess and describe your body composition. Three times during the study, you will have a Uniform Isotope Source (UNIS). Your muscles, organs and bones contain potassium-40, a naturally occurring radioisotope of potassium not found in fat. By counting the potassium-40, we will be able to estimate your fat-free mass and body cell mass and determine whether it changes with the boron in the diet. During this whole-body count, you will be exposed for approximately one minute to a small amount of radiation from sodium-22 (a radioactive form of sodium) contained in a sealed-sheet of plastic (UNIS) under the mattress in the whole-body counter. This will permit us to determine your self-absorption of internally-produced radiation because of your particular body size and shape. Before each whole-body count, you will shower, shampoo your hair and put on clothing, which we will supply. A

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technician will direct you into the whole-body counter steel room where you will lie down on a mattress on the counter. During a whole-body count and UNIS, you will stay in the enclosed steel room, lying on a bed between two banks of 16 detectors each. You will be observed on a closed-circuit TV system, will be able to contact the technician by intercom, and you will have a choice of listening to the radio, cassette tape player or having silence. Each whole-body count and UNIS will take a total of 10-30 minutes including data processing time.

Anthropometry: These measurements are used to evaluate the adequacy of your dietary energy intake. Determination of circumferences of the upper arm, calf, thigh and waist, and of length measurements at the elbow and the knee will be made by using a tape measure and an anthropometric caliper. Assessments of skinfold thickness will be performed by pinching the skin, holding the pinched area, then measuring the thickness of the pinched skin and adipose tissue at the front and back of your upper arm, back, waist and calf. Standing height and body weight will also be determined. These anthropometric measurements will be performed 3 times during the study. You will wear loose-fitting clothing.

Bioelectrical Impedance: Measurements are made for validation of this technique to predict body composition and fluid distribution in postmenopausal women. Bioelectrical impedance measurements performed to determine fat and muscle in the body three times during the study. You will lie on a cot and electrodes will be attached to your wrists, ankles, elbows, knees, upper and lower arm, and thigh. A painless, low energy electrical current of 100 microamps at radio frequencies ranging from 1 kilohertz to 1 megahertz will be applied. This radiofrequency current is the same amount of electrical current that floats around you while you are watching television or listening to the radio. You will not be aware that the electrical current is

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entering your body. Various measures of how your body conducts this electrical current will be determined. You will wear your own shorts and a short sleeved shirt or t-shirt but no shoes or socks.

Do Living Conditions Represent A Risk?

No, despite the minimal loss of privacy normal in any group living situation and some loss of freedom as demanded by the study regime, the Metabolic Unit environment and study procedures have been designed so participation does not present any risk to your physical or psychological health. To assist in your adjustment to the study and the special demands of group living, you will be expected to attend weekly group meetings with the Metabolic Unit Manager and Psychology staff and to periodically meet individually with the Psychologist or a Graduate Psychology assistants.

What Are The Risks Of The Study?

RA Therapies: The RA therapies that are continued in the study are very specific therapies that were either prescribed by a physician or selected by you before entry into the study. It is your responsibility to be aware of the positive and negative effects that those therapies have on your health. There are no known risks associated with consuming the diet and supplements prepared for the study while continuing any of the methotrexate, prednisone, nonacetylated salicylates, or hormone replacement therapies (see chart on pages 3-5). Because methotrexate interferes with the vitamin, folic acid, extra amounts of folic acid (1 milligram per day) will be supplemented to the diet.

Low Boron Diet: Negative boron balance has been induced experimentally with normal diets that supplied about 0.36 milligram boron daily. Previous studies at the Grand Forks Human

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Nutrition Research Center (GFHNRC) indicate that persons consuming 0.36 milligram of boron daily for about three months, compared to when they received 3.23 milligram of boron daily for the same period of time reported no noticeable effects, but did have small but significant decreases in systolic and diastolic blood pressure within the physiological range and a lengthened segment of the heart beat tracing, and blood and urine biochemical changes. During the boron depletion period of this study, you will be consuming about 0.2 milligram of boron daily for 77 days.

Symptoms of boron deficiency in humans are not well defined. Associations have been made between low boron intake and the incidence of arthritis. Because you will be consuming a diet low in boron for part of the study, it is expected that you will show some changes in the amounts of boron and minerals, and some organic substances in your blood, urine and stools, and increased incidence and severity of signs associated with rheumatoid arthritis, mainly pain and inflammation of the joints.

You could also show some small changes in your brain electrical activity or heart beats. We anticipate that these changes will not be noticeable to you and will not be health-threatening. As a precaution, you will be closely monitored for any severe or health threatening signs of boron deprivation (including heart beat changes) and will be supplemented with boron or examined by a study physician for complications of rheumatoid arthritis if such signs occur at no cost to you.

There is a small possibility that heart rhythm (your heart beat) change might occur. As indicated, your heart will be monitored routinely by a heart beat recorder machine during the study. If any abnormalities or significant changes in your heart beats or heart structure occur

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which indicate that you may become at risk if the boron depletion were to be continued, you will be supplemented with boron and will stay on the boron supplementation until the end of the study. In addition, any other evidence of the possibility of developing severely low boron status that could be harmful to you will be cause for stopping boron depletion and starting boron supplementation.

If an RA flare-up occurs, you will be advised to consult your personal physician who is familiar with your arthritis history by phone and/or written correspondence. With your written permission, health-related or pertinent research information collected during the course of the study will be provided to the consulting/personal physician. Travel to a consulting/personal physician (that may be the same as the study physician) within a 100 mile radius of Grand Forks, ND, will be provided by the Research Center. If beyond a 100 mile radius, it will be suggested that the physician coordinate with the health care center associated with the study physician. With your written permission, your consulting/personal physician will be advised of the RA treatments approved for use during the study. The actual treatment for a specific flare-up may include treatments other than those suggested. If the flare-up or treatment interferes with the research, you will be dismissed from the study. If the flare-up does not interfere with the research, then continuation will be at your discretion.

Experimental Diet: Every effort has been made to plan tasty diets acceptable to you; however, you may become tired of consuming the same limited number of foods every third day or 168 days. All foods are from local stores, and the foods are prepared in standard ways. Any supplements may be added to ensure that all nutrients (except perhaps boron) are in the amounts estimated to be consumed by postmenopausal women near your age. There are no

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known risks associated with consumption of broccoli grown in a solution containing mainly just one natural boron isotope other than possible transient intestinal gas and bloating associated with broccoli consumption per se.

Cardiac Monitoring: There are no known risks associated with heart monitoring or 12-lead electrocardiograms. However, you may experience some skin irritation from contact with the electrodes.

RA Feature Assessment: All assessments of joint function are expected to cause a transient increase in pain in joints with active rheumatoid arthritis. There are no known risks associated with determining hand volume by immersion in water.

Resting Energy Expenditure: There are no known risks associated with participating in the test to determine how much energy you use up while resting. You may experience some minor discomfort with the equipment used to collect your breath.

Blood Draws: There will be some discomfort as the needle enters your skin. About 10% of the time a small bruise (hematoma) develops at the puncture site. Less than 0.1% of the time the site may become infected, but this is easily treated with antibiotics. If an infection develops, the GFHNRC will pay for all necessary medical care and attention. A maximum of 287 milliliter (0.6 pints) will be drawn within an eight-week period. This is considerably less than blood bank donation limits of 475 milliliter (1 pint) every eight weeks.

The initial condition of rheumatoid arthritis sometimes causes slight anemia (less than 10 grams of hemoglobin per deciliter of blood). A study with men and women with inflammatory arthritis found that their hemoglobin values were 12.6 ± 0.6 grams per deciliter of blood. Normal hemoglobin for women between 18 and 49 years of age is 12-16 grams per deciliter of blood.

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The amount of blood that you will give is not likely to markedly affect your iron status. However, if your initial hemoglobin is at or above 10 grams per deciliter of blood and if the removal of blood causes the amount of hemoglobin in your blood to drop below 10 grams per deciliter of blood, the amount of blood taken from you will be decreased. Or, if your initial hemoglobin is below 10 grams per deciliter of blood and if the removal of blood causes the amount of hemoglobin in your blood to drop more than another 10%, the amount of blood taken from you will be decreased. If you become very anemic (very iron deficient), you will be sent to a local physician at no cost to you. If the physician prescribes iron, you will be provided supplements. If you are still iron depleted at the end of the study, three months of iron supplements will be given to you to make sure your iron status returns to your usual level.

Boron Stable Isotope Administration: The procedure of inserting a needle in an arm vein which will stay there for 4 hours is similar to that used routinely in hospitals and clinics to diagnose diabetes mellitus. There should be minimal risk and discomfort. There is no known risk for eating broccoli raised in regular greenhouse in a mineral water solution.

Urine and Stool Collection: There are no known risks associated with this procedure. There may be odors from the urine and stool collections. This can be minimized by keeping the samples cool in the refrigerator in your bathroom.

Brain Function: There are no known risks associated with the electroencephalogram or the collection of other electrophysiologic data related to polysomnography. However, you may experience mild, transient discomfort during electrode placement on or removal from the scalp, face, neck and legs.

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Psychological and Behavioral Function: There are no known risks or discomforts associated with assessment of sensory-motor and spatial skills, cognitive processes, motor tremor, mood states, or other behaviors and symptoms assessed by questionnaires. If you have any concerns regarding psychological and behavioral assessments, you may discuss these with the psychologist or psychology research assistants (supervised by a licensed clinical psychologist), with whom you will be meeting on a regular basis.

Activity Monitoring: There are no known risks or discomforts associated with activity monitoring.

Vision and Auditory Function: There are no known risks or discomforts associated with the vision or hearing tests.

Dual X-Ray Absorptiometry and Whole-Body Scintillation Counting: Exposure to radiation is often expressed in terms of rem or millirem (one thousandth of a rem). By participating in this study, the total amount of extra whole body radiation you will receive is approximately 1.5 millirem, or about a half of 1% of the average annual radiation exposure of 360 millirem per person in the U.S. This amount of total radiation is less than 15% of a routine chest x-ray. It is equivalent to spending 8 hours in a jetliner at cruising altitude or spending approximately 1.5 weeks in the Colorado plateau area. It is about equal to radiation exposure from cosmic rays at sea level for 3 weeks. Two concerns about radiation are that it can cause cancer or shorten life. Estimates of the risk of radiation have been based mainly on very high radiation exposures of Japanese survivors of World War II atomic bombs. If the effect of radiation at high doses is assumed to be proportional to the effect at low doses, the radiation exposure received in this study could result in 0.125 "extra" cancer deaths per 100,000 people

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and reduce life span by an average of 11.5 minutes per person. However, it is impossible to accurately estimate the excess deaths because the exposure from participating in this study is insignificant when compared to a person's lifetime exposure of about 24,000 milligrams from natural sources such as cosmic rays and radon.

Anthropometry and Skinfold Thickness Measurements: There are no known risks involved in the anthropometric and skinfold thickness measurements. Some individuals, however, may experience transient, minor discomfort during the measurement of skinfold thickness.

Bioelectrical Impedance: There are no known biological or health hazards associated with the method and procedure to be used to measure how your body conducts an applied, non perceptible, low level, safe electrical current.

Adverse Reactions or Health Problems: Adverse reactions are unlikely, and but could include problems such as food intolerance, faintness with blood draws, or common health care problems unrelated to the research, such as infectious illnesses, muscle strain, physical injuries, or previously unrecognized health problems. Any detected difficulties will be discussed with you individually. You may be advised to consult with a local physician, at the expense of the research center if related to the research or at your own expense if unrelated to the research. If we initiate the medical consultation, we will pay transportation costs within a 100-mile radius of the Center. If you are unwilling to see a physician within that 100-mile radius limit, you will most likely be dismissed from the study. No health-related information will be provided to a health care center without your express written consent. If the problem interferes with the research, or if you no longer qualify under the medical or RA treatment criteria, then you will be

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dismissed from the study. If the problem does not interfere with the research, then continuation will be at your discretion. Temporary changes in procedures (e.g. missed or delayed meals or testing) may be possible if they do not interfere with the main objective of the research, but you will always have the option to withdraw.

How Are Emergencies Handled?

A nurse is on the Unit twenty-four hours a day, seven days a week. A physician is on staff. The nurses are CPR certified and the physician is certified in Advance Cardiac Life Support. The Altru Health System's ambulance (located 1 mile away) will be called for emergency medical care. First aid supplies and a fire extinguisher are on the Unit. Policies and procedures for Emergency Response (including fire, bomb threats, and tornado) are in place.

Are There Benefits To Taking Part In This Study?

Direct benefits include the satisfaction from participating in a worthwhile research study that will benefit humanity because it will advance knowledge about the importance of boron for health and well being, especially as it relates to the control of rheumatoid arthritis. Information may be used to plan better diets or to change the dietary recommendations for boron. In appreciation for your participation, you will receive \$35 per day to be paid every two weeks. The total amount of the honorarium that you will receive if you complete the study will be \$5,880.

What Other Choices Do I Have If I Don't Take Part In This Study?

This study is being done only to gather research information. You may choose not to take part in this study.

What Are The Costs Of Tests And Procedures?

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We do not expect that you will have to pay any money if you are in this study. There are no additional costs to you as a result of participating in the study.

What if I Decide Later Not To Take Part In This Study?

You are free to leave this study at any time; however, if you leave early for any reason, you forfeit any unearned stipend. We reserve the right to dismiss you at any time if, in our opinion, you have disobeyed regulations, have disrupted research or have exhibited inappropriate behavior. If it is felt that continuing in the study might be harmful to you physically or mentally, or if there is the development of an illness or a condition that might affect research results, you will be dismissed from the study. Regardless of the reason for leaving the study, you will receive the honorarium to the day of discharge. Early dismissal or withdrawal from the study will not be held against you by the University of North Dakota, the U.S. government, nor your personal physician.

What Happens If I Am Injured Because I Took Part In This Study?

If you are injured while participating in this study as a result of the negligence of an involved United States Government employee, you may be able to receive compensation for your injury in accordance with the requirements of the Federal Tort Claims Act. Compensation from individuals or organizations other than the United States might also be available to you. If you are a federal employee acting within the scope of your employment, you may be entitled to benefits in accordance with the Federal Employees Compensation Act.

During your participation in this nutritional study, medical care will be available from physicians in the local community. You are responsible for any and all expenses related to

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medical care involved with health problems, including rheumatoid arthritis, whose cause and origin predate entry into this study. Other routine medical expenses incurred to maintain your health during your participation in the experimental protocol will be provided without cost to you. Because of the lack of total health care coverage, you are strongly encouraged to maintain any personal health care insurance throughout the time of your participation.

You can get more information on our policies, the conduct of this study, and your rights as a research subject by calling Dr Curtiss Hunt at 701-795-8423.

What About Confidentiality?

All information about you (other than your name, address and social security number which are needed to prepare your IRS Form 1099) is confidential. We do not withhold income, social security or unemployment taxes because we do not consider you to be an employee.

To keep your research data confidential, you will be assigned an identification number which will be used to anonymously code your research data for computer entry. Paper copies of your personal information and medical data will be kept in a locked file, with access limited to approved staff members. Your signed consent form will be kept in a locked file for at least 3 years, and our current policy is to keep them indefinitely. If and when they are disposed of, your name and any identifying information will be shredded. Any results from your participation in this project may be published in a scientific journal, but only in a form not identifiable with you.

At the conclusion of your participation in the study, you may request that copies or summaries of your test results be sent to a qualified professional for interpretation and review with you at your own expense. A fee may be charged to cover reproduction expenses if large quantities of data are requested.

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Who Can Answer My Questions?

You are free to ask questions at any time during the study by calling Dr. Curtiss Hunt at 701-795-8423 or -8353, Dr. James Penland at 701-795-8471 or -8353, Dr. Joseph Sleckman at 701-280-8900, or Dr. Henry Lukaski at 701-795-8429 or -8353, or by talking to any staff member.

I Agree To Take Part In This Study.

I have been given a signed copy of this form. My signature below signifies that I have read this form, have had the study explained, have had any questions answered to my satisfaction, and that I now understand what will be expected of me.

Participant

Date

Witness

Date

Investigator

Date

Revised 11-15-00

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APPENDIX D

VERBAL COMMANDS FOR RANGE OF MOTION ASSESSMENT

For the following measurements, a pressure of moderate intensity will be applied to subjects for consistent readings in measurements. Deviating from standard range of motion measurement procedures, if hypermobility exists measurements will be taken from the palmar surface of the digit.

FIRST DIGIT MEASUREMENTS

MP Flexion

Testing position: Weight of the hand will rest on the 5th metacarpal and phalange, with wrist in neutral position.

Verbal cues: “Bend your thumb as far as you can, like this.”

Demonstration provided by tester. “Can you go any further?”

MP Extension

Testing position: Weight of the hand will rest on the 5th metacarpal and phalange, with wrist in neutral position.

Verbal cues: “Straighten your thumb as far as you can like this.”

Demonstration provided by tester. “Can you go any further?”

IP Flexion

Testing position: Weight of the hand will rest on the 5th metacarpal and phalange, with wrist in neutral position.

Verbal cues: “Bend your thumb as far as you can, like this.”

Demonstration provided by tester. “Can you go any further?”

IP Extension

Testing position: Weight of the hand will rest on the 5th metacarpal and phalange, with wrist in neutral position.

Verbal cues: "Straighten your thumb as far as you can like this."

Demonstration provided by tester. "Can you go any further?"

SECOND THROUGH FIFTH DIGITS' MEASUREMENTS

MP Flexion

Testing position: Arm placed in approximately 10 degrees of shoulder flexion and abduction, 55 degrees elbow flexion, 45 degrees wrist pronation, with the palmar surface of the hand resting on the table.

Verbal cues: "Bend your finger down toward the ground like this."

Demonstration provided. "Can you go any further?"

MP Extension

Testing position: Arm placed in approximately 10 degrees of shoulder flexion and abduction, 55 degrees elbow flexion, 45 degrees wrist pronation, with the palmar surface of the hand resting on the table.

Verbal cues: "Straighten your finger towards the ceiling as far as you can go." Demonstration provided. "Can you go any further?"

PIP Flexion

Testing position: Arm placed in approximately 10 degrees of shoulder flexion and abduction, 105 degrees of elbow flexion, wrist in neutral position, with the dorsum of hand facing tester.

Verbal cues: “Bend your middle knuckle as far as you can. Be careful not to inhibit your ROM by stopping when you come in contact with your palm.” Demonstration provided by tester. “Can you go any further?”

PIP Extension

Testing position: Arm placed in approximately 10 degrees of shoulder flexion and abduction, 105 degrees of elbow flexion, wrist in neutral position, with the dorsum of hand facing tester.

Verbal cues: “Straighten your finger as much as you can.” Demonstration provided. “Can you go any further?”

DIP Flexion

Testing position: Arm placed in approximately 10 degrees of shoulder flexion and abduction, 105 degrees of elbow flexion, wrist in neutral position, with the dorsum of hand facing tester.

Verbal cues: “Bend the knuckle closest to the tip of your finger as far as you can. Be careful not to inhibit your ROM by stopping when you come in contact with your finger.” Demonstration provided by tester. “Can you go any further?”

DIP Extension

Testing position: Arm placed in approximately 10 degrees of shoulder flexion and abduction, 105 degrees of elbow flexion, wrist in neutral position, with the dorsum of hand facing tester.

Verbal cues: "Straighten your finger as much as you can." Demonstration provided. "Can you go any further?"

WRIST MEASUREMENTS

Flexion

Testing position: Arm placed in approximately 10 degrees of shoulder flexion and abduction, 55 degrees elbow flexion, 45 degrees wrist pronation, with the hand resting off the edge of the table, just proximal to the ulnar styloid process.

Verbal cues: "Bend your wrist down towards the floor as far as you can go, keeping your fingers straight." Demonstration provided. "Can you go any further?"

Extension

Testing position: Arm placed in approximately 10 degrees of shoulder flexion and abduction, 55 degrees elbow flexion, 45 degrees wrist pronation, with the hand resting off the edge of the table, just proximal to the ulnar styloid process.

Verbal cues: "Can you bend your wrist up to the ceiling as far as you can with your fingers straight." Demonstration provided by tester. "Can you go any further?"

Ulnar Deviation

Testing position: Arm placed in approximately 10 degrees of shoulder flexion and abduction, 55 degrees elbow flexion, 45 degrees wrist

pronation, with the hand resting off the edge of the table, just proximal to the ulnar styloid process.

Verbal cues: “Can you move your hand as far as you can to the side of your little finger moving at the wrist joint only.” Demonstration provided by tester. “Can you go any further?”

Radial Deviation

Testing position: Arm placed in approximately 10 degrees of shoulder flexion and abduction, 55 degrees elbow flexion, 45 degrees wrist pronation, with the hand resting off the edge of the table, just proximal to the ulnar styloid process.

Verbal cues: “Can you move your hand as far as you can to the side of your thumb moving at the wrist joint only.” Demonstration provided by tester. “Can you go any further?”

APPENDIX E

POLYARTHRITIS ASSESSMENT

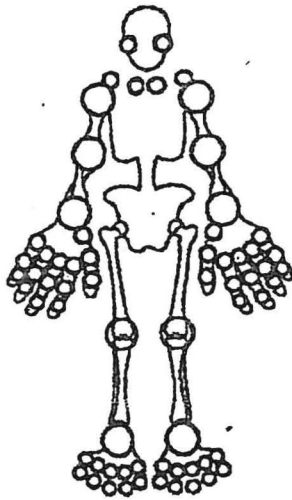
Patient's Name _____ Assessment Date _____

Duration of morning stiffness, in hours _____

Number of active joints _____

Please indicate on the diagram below by placing an "X" or a circle in the area in which you are feeling activity within the joint.

Active Joints



Joint Pain Now (Circle number):

No Pain: 0—1—2—3—4—5—6—7—8—9—10: Worst Possible Pain

"Fibromyalgic" Point Count

	Point Count	
	<u>Right</u> <u>Left</u>	
	Occiput	_____
	Trapezius	_____
	Supraspinatus	_____
	Low neck	_____
	2nd rib	_____
	Inner knee	_____
	Outer elbow	_____
	Gluteus	_____
Trochanter	_____	
Total (of 18) _____		

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